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VOL. 34, NO. 1 JULY, 1960

Twenty-fifth Annual Convention
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23, 24, 25, 26 October 1960

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1. Weiss, E., and English, O.S.: Psychosomatic Medicine, p. 254, W.B. Saunders Company, Philadelphia, 1957. 2. Bodi, T., et al.: Am. J. Gastroent. 29:643 (June) 1958.

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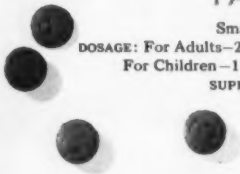

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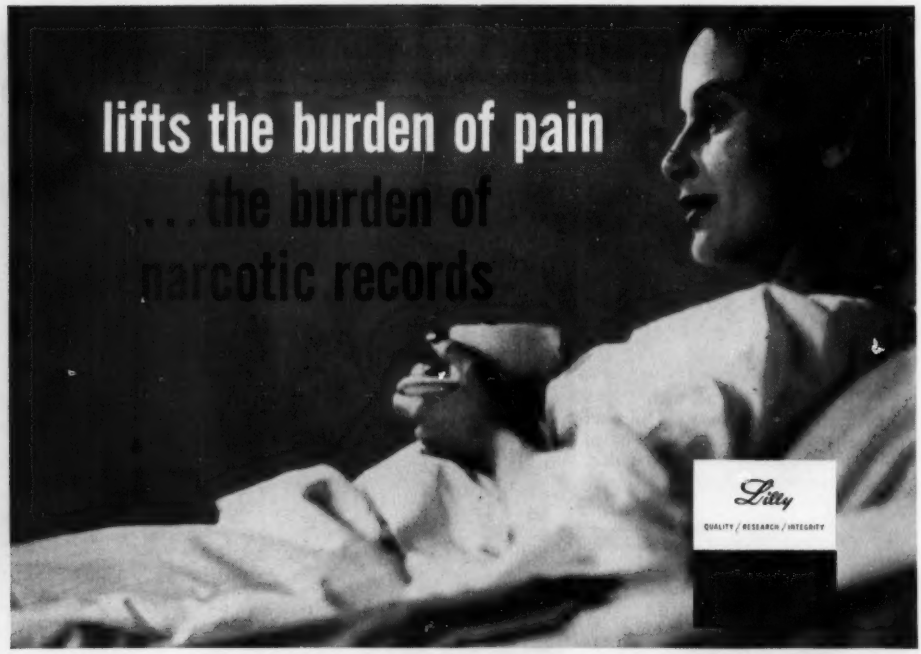

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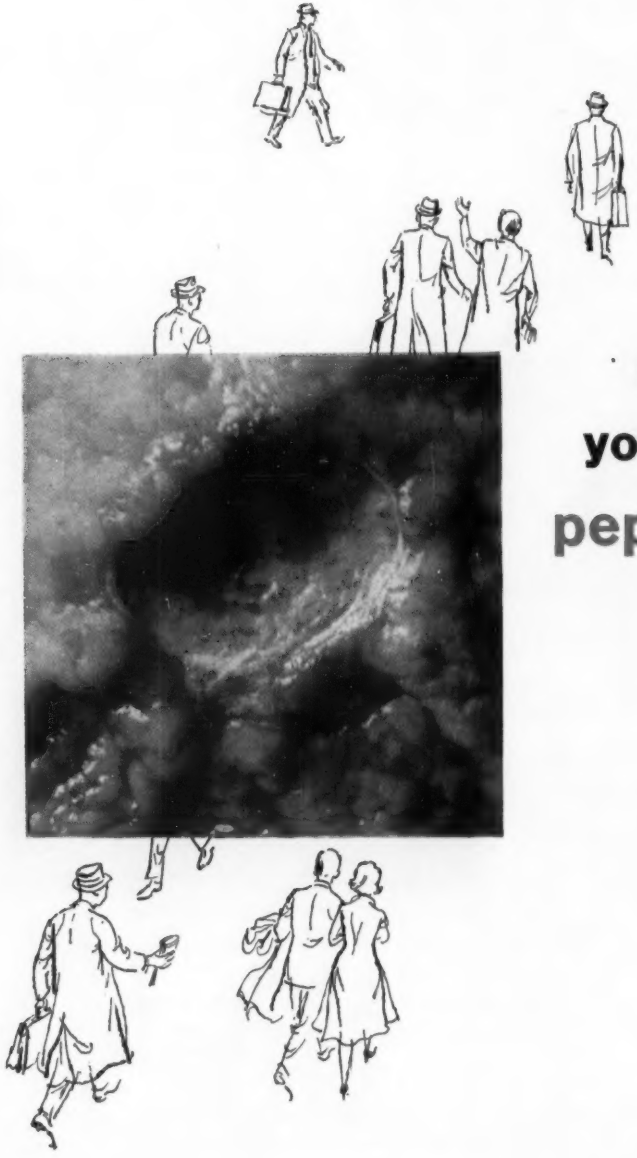

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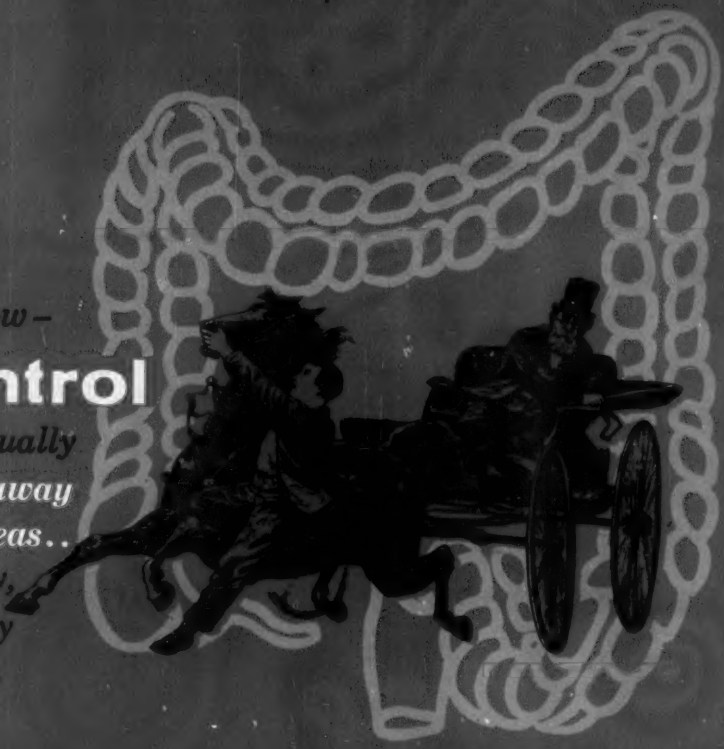

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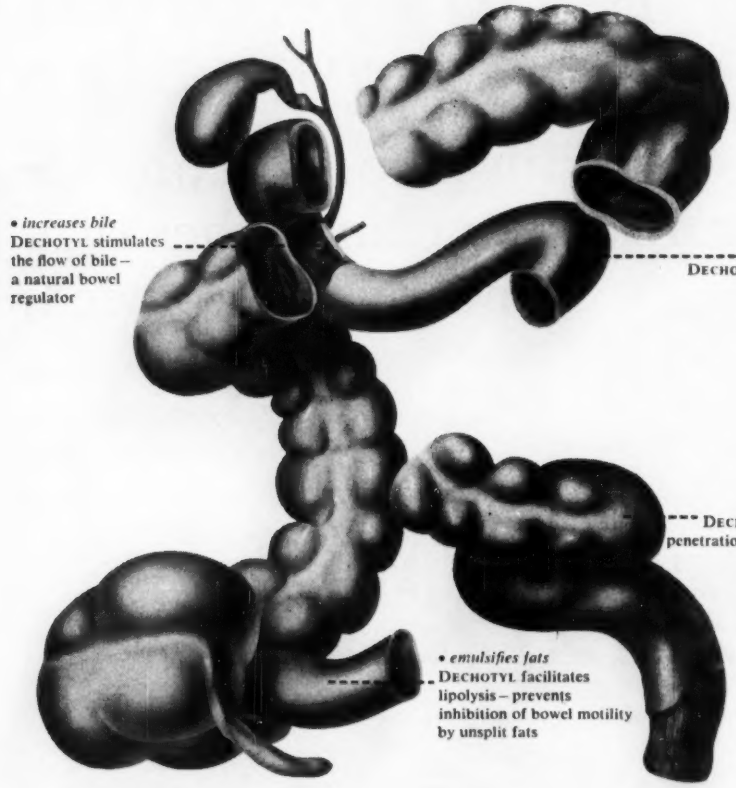

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VOLUME 34 JULY, 1960 NUMBER 1

CHEMOTHERAPY IN THE MANAGEMENT OF MALIGNANCIES OF THE GASTROINTESTINAL TRACT*

JOHN B. FIELD, M.D., Ph.D.

Los Angeles, Calif.

A staggering mortality of from 70 to 100 per cent is reported for malignant lesions of the gastrointestinal tract[1]. This awesome statistic has been a stimulant to a surge of investigation in newer directions. The more radical efforts of surgical excision and resection as well as the newer devices for applying intensive ionizing radiation have not, however, unfortunately, been particularly successful in improving the overall mortality records. These circumstances have helped to develop an increasing interest in the newer discipline of chemotherapy. The purpose of this brief report, therefore, is to summarize the present status of this dynamic but infant subject.

The chemotherapeutic management of lesions of the intestinal tract now have taken two directions. One is the use of specific agents in an effort to offer palliation for treatment failures following surgery and/or radiation therapy. The second is in the use of agents in conjunction with surgery and to improve the surgical statistics. Since the aforementioned is in the exploratory stages it is, as yet, impossible to present tabulations of satisfying results or to otherwise demonstrate improved survival data. In the main this discussion will deal with early observations of the effects of certain chemical agents on malignant lesions of the gastrointestinal tract and the response of a limited series of patients.

Chemotherapeutic agents available:—A variety of agents have been studied during the past decade. Only several merit consideration. In the main only two types have proven of usefulness. The major group is that of the alkylating agents which includes the nitrogen mustard [methyl-bis (beta-chloroethyl) amine hydrochloride], triethylene melamine (TEM) and triethylene thiophosphoramide

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Los Angeles, Calif., 24, 25, 26 September 1959.

From The Department of Medicine, University of Southern California School of Medicine and the Los Angeles County Hospital and The Mount Sinai Hospital, Los Angeles, Calif.

(thio-TEPA). A newer and apparently more promising agent is 5-fluorouracil. From the limited information available about mode of action and clinical results it would appear that most of the older as well as the newer alkylating agents are similar in effect and there is little reason to believe that any particular agent has a specific preference for any specific tumor type. In our experience we tend to rely primarily upon the original methyl-bis (beta-chloroethyl) amine hydrochloride (known commercially as Mustargen and hereafter referred to as nitrogen mustard). This is given primarily intravenously or into body cavities and its noxious side-effects are now easily controlled by simple technics[2]. For office dispensing we prefer TEM since it is conveniently available in tablet form. When either alkylating agent is given in a single large dose with heavy barbiturate sedation, disturbing nausea and emesis are reduced to tolerable levels. Nitrogen mustard is also delivered through arterial catheters into regions of tumor concentration. This technic permits a more efficient tumor exposure to drugs and occasionally a more gratifying result. 5-fluorouracil is given intravenously over a period of days and with proper precautions, untoward reactions such as stomatitis, diarrhea and leukopenia can be minimal.

Palliative therapy of inoperable or metastatic disease:—The site and histological type of primary neoplasm is of considerable importance in determining the feasibility and choice of chemotherapy. A more favorable prognosis obtains with the category of neoplasms encompassed by the title of "malignant lymphomas" which includes Hodgkin's disease and the several forms of lymphosarcoma. It occasionally arises as a primary unicentric tumor of the stomach or more frequently in the small intestine and most commonly, as an accompaniment of a generalized lymphoma. This disease complex is especially sensitive to many chemotherapeutic agents, particularly the alkylating agents.

Lesions of the esophagus remain, to our knowledge, as completely recalcitrant to any chemotherapy as they are to the conventional therapeutic attack by the surgeon or radiologist. In dealing with carcinoma of the stomach the outlook has remained almost as bleak excepting that occasionally an objective change suggesting carcinolytic activity by some drug has been observed. Bateman[3] has reported that 2 of 14 patients treated with some form of chemotherapy have demonstrated a palpable reduction in tumor size. Similarly we have had reduction of the tumor mass in 2 of 21 patients with carcinoma of the stomach treated with nitrogen mustard. The duration of remission was relatively brief, persisting 6 weeks to 3 months before the disease resumed its inexorable course. The preliminary data obtained with 5-fluorouracil represents some improvement. From a number of clinics the latest summary indicates that 16 of 65 cases have had an objective response.

In inoperable or metastatic carcinoma of the colon there is insufficient evidence of uniform inhibition of tumor growth by nitrogen mustard or its analogs. Yet individual therapists have demonstrated cases of prolonged survival

of 3 and more years where the agent has been intensively and diligently applied[3]. We have under observation at least 3 cases of carcinoma of the colon with intraabdominal and hepatic metastases who are being maintained in good health 3 to 5 years with TEM given usually once monthly.

The recent advent of 5-fluorouracil presents what appears to be a dramatic advance in the control of disseminated carcinoma of the colon and rectum. Objective reduction of tumor mass has been reported in 58 of 224 patients. Although the initial response of a significant number is impressive and in many instances prolongation of life in near-terminal patients has been observed, it is, as yet, obviously premature to draw further conclusions. The remissions induced in our personal series are brief unless the drug is given almost continuously. We have maintained 2 of 7 cases of advanced metastatic carcinomas of the colon with marked objective improvement for almost 5 months.

The administration of 5-fluorouracil is relatively simple and hospitalization is not required. It is given intravenously to an average patient at a level of 15 mg./kg. daily for 5 successive days. If no toxicity is observed, 7.5 mg./kg. are given on the 7th, 9th, 11th and 13th days unless toxicity occurs before then. In some cases we have found it to be necessary or advantageous to maintain control of an advanced malignant state by administering a continuing course of the drug with one injection of from 7.5 mg. to 15 mg./kg. weekly. The most common reactions to the drug are stomatitis, diarrhea, leukopenia and thrombocytopenia and in general they do not occur until after the fifth or sixth injection.

The chemotherapy of patients with carcinomas of the biliary tree and pancreas is almost uniformly disappointing.

Control of malignant effusions:—A frequent concomitant of metastatic carcinoma of the colon and stomach is the appearance of effusion provoked by dissemination of malignant cells over the peritoneal surfaces. The urgency of inhibiting the recurrence of fluid with attendant exhaustion of the patient both by repeated paracenteses as well as loss of vital body protein is well recognized. The instillation of 10 to 30 mg. nitrogen mustard into the abdominal cavity is a simple, inexpensive procedure which appears to be supplanting the use of radioactive isotopes. The mustard is at least the equal of the latter in suppressing ascites but requires no instrumentation or special precautions. Treatment can be repeated often so long as leukopenia does not exist.

Chemotherapy as an adjunct of surgery of tumors of the stomach and colon:—Dissemination of cancer cells during manipulation of tumors of the gastrointestinal tract has been proven by actual observation of malignant cells and emboli in circulating venous blood and in smears taken from the surgical area[4]. The high incidence of local recurrence and in the suture line in resections of the colon may be due to implantation during surgery[5]. In a relatively high incidence of cases (up to 30 per cent) wound washings of patients with malignancies have

revealed tumor cells. It has been claimed that wound irrigation with an organic derivative of hypochlorous acid (Chlorpactin XCB) has merit in destroying viable tumor cells capable of causing local recurrence[6]. Cole and associates[7] designed an original study which proved that the administration of nitrogen mustard reduced the metastatic spread of an experimental tumor introduced into the vein of rats and prolonged their lives. During the past few years, in a number of clinics, the surgery of tumors of the stomach or colon is routinely accompanied by the instillation of nitrogen mustard[1]. This is done generally by introducing 0.1 mg. per kg. of body weight into the major vein, a similar amount well-diluted in saline solution into the peritoneal cavity, and another 0.2 mg. per kg. given into a peripheral vein in single or divided doses within the following 24 hours. If the patient is not debilitated and the leucocyte count is at least 6,000, untoward effects are minimal. Small amounts of nitrogen mustard over wound surfaces do not interfere with granulation and healing[8].

On a hypothetical basis it appears that this approach is well-founded and should increase the effectiveness and cure rate of the tumor surgeon. Modifications of the basic technic and newer tumorcidal agents should benefit the end results. At this state, however, the clinical data is premature. Thus it cannot yet be predicted that a major improvement of the survival statistics is at hand.

Summary

1. The alkylating agents, particularly nitrogen mustard, are effective in control of malignant lymphomas of the gastrointestinal tract.

2. Rarely an inoperable or metastatic carcinoma of the stomach may be temporarily controlled with nitrogen mustard and survival may be slightly improved in carcinoma of the colon treated with alkylating agents as triethylene melamine.

3. The recent use of 5-fluorouracil has improved the incidence of objective response of inoperable carcinoma of the stomach but particularly with carcinoma of the colon. The duration of control is, however, as yet unknown.

4. Ascites induced by cancer of the stomach and colon can frequently be controlled by the instillation of nitrogen mustard.

5. It is possible that the adjunctive use of nitrogen mustard with surgery of cancers of the stomach and colon may ultimately improve the effectiveness and cure rate of the tumor surgeon.

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DIFFERENTIAL DIAGNOSIS OF JAUNDICE*

ALEXANDER WALLACE, III, M.D., F.A.C.G.

Los Angeles, Calif.

Certainly I feel that you will all agree that we cannot progress through a gastrointestinal conference without a discussion of the perennial topic of the "Differential Diagnosis of Jaundice", and I shall not decry the limitation of time in the presentation of such a subject.

My approach is to attempt to illustrate by means of case reports several of the more difficult diagnostic jaundice problems we have encountered recently, stressing the features of differential diagnosis.

If we were to analyze briefly the example of viral hepatitis, we realize that we cannot depend upon the virologist, epidemiologist, or even pathologist for an unequivocal diagnosis. The virus has not been identified microscopically or serologically. Histologic changes present in the liver, which though more specific cannot be considered unequivocal evidence of hepatitis, particularly in the more unusual and late forms of the disease in which the morphologic features are less distinctive. Liver function tests, although often highly specific and characteristic, are again not diagnostic, so in order to establish a diagnosis we are left with an evaluation of the sum total of the clinical, historical, physical and laboratory means at hand.

I trust that you all have a copy of the abbreviated case reports, and we shall attempt to read them to you going over some of the details briefly.

Case 1:—This is a 53-year old female who presented a history of "influenza" of four weeks' duration, characterized by fever, arthralgia, extreme fatigue, and associated with depression. Two weeks previously she had noted dark urine, chalky stools, and the onset of jaundice. During her illness a weight loss of 7 pounds was experienced, and six days prior to entry to the hospital pruritus had developed. No abdominal pain occurred at any time. There was no medication history.

Physical examination revealed jaundice and a palpable liver two finger-breadths distal to the right costal margin.

Laboratory determinations: Hemoglobin, 12.2; W.B.C., 6,000. Differential: Neutrophils, 65; Lymphocytes, 27; Eosinophils, 8. Urine showed a trace of bile. Serum bilirubin, 3.8/7.7. Transaminase 150 (SGOT). Thymol turbidity, 2. Alkaline phosphatase, 16.6. NPN, 27. C.F., negative. An upper gastrointestinal examination was negative. Three weeks later serum bilirubin was 0.7/2.1; SGOT, 30.

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Los Angeles, Calif., 24, 25, 26 September 1959.

At this point surgical consultation was obtained and a tentative diagnosis of obstructive jaundice was made.

(Slide) This projected 25 mg. Thorazine tablet represented the best liver function test available. As I said initially the medication history was not obtained, and only after protracted questioning of the patient was it determined that approximately three weeks prior to her illness she had taken eight of these tablets and then discontinued their use, so that an incubation period of approximately two weeks had occurred.

(Slide) This is a photomicrograph of a liver biopsy performed on this patient, and shows the characteristic features of central lobular bile staining, and you will notice the bile casts in the canaliculi. There is no evidence of periportal inflammation.

The key to the diagnosis in this case was the careful history which was difficult to obtain. An additional diagnostic feature which is often not stressed is the peripheral eosinophilia which may be transient in patients with chlorpromazine hepatitis. Another feature in this case that was of significant interest and concerned the surgeon was the amount of weight loss experienced by the patient. A total weight loss from onset of disease until after the liver biopsy obtained, was 13 pounds, and this is not actually too unusual in hepatitis, and for that matter also in common duct stone, and is often a cause for a mistaken diagnosis.

Dr. Snell and his group had proposed that the serum glutamic pyruvic transaminase test is apparently more sensitive than the SGOT test in hepatitis. We have not had any experience with that and cannot comment on it.

An additional motive in presenting chlorpromazine hepatitis is based on the increasing frequency of cases reported, and particularly the more recent examples of protracted jaundice occurring in patients receiving these drugs. Some of the jaundice cases, as in Hofbauer's series persisting for 20 and 24 months, and more recently two cases of hypercholesteremic cirrhosis persisting months after the original chlorpromazine hepatitis. The gastroenterologist would certainly seem to have an axe to grind with regards to the indiscriminate use of these potent drugs.

Case 2:—A 56-year old male, one month complained of light stools, one week fever, chills, diffuse abdominal cramping, temperature of 104 degrees F.

On examination acutely ill. Liver was tender 5 fingerbreadths palpable from right costal margin. A palpable spleen and ascites was noted.

Laboratory determinations: Hemoglobin of 10.5; W.B.C., 12,000. Serum bilirubin of 5.7/11.6. A three to four plus C.F. Thymol turbidity, 21.5. Alkaline phosphatase, 40. Glycosuria was noted, but a blood sugar determination was within range of normal. An upper gastrointestinal examination was negative.

Treatment consisted of transfusions, steroids, antibiotics, intravenous glucose. In two months his serum bilirubin had returned to an almost normal level. Approximately six months later the onset of diabetes occurred, requiring 50 units of NPH insulin daily.

In 1958, three years later, diffuse skin pigmentation was noted. A serum iron was obtained which was reported at 140 (Normal values, 65-175). Total iron binding capacity 413 (Normal values 252-410). BSP retention, 45 per cent in 30 minutes. Prothrombin time, 45 per cent. A/G, 3.2/3.4. A liver biopsy was performed.

(Slide) This photomicrograph of the liver biopsy shows iron deposits in the hepatic parenchymal cells and also the cholangiolar cells. The remainder of the liver biopsy shows the characteristic findings of cirrhosis.

This man also had a skin biopsy, but since the site of the biopsy was the pretibial site, and since this is a frequent location of trauma, hemosiderin deposits are not as diagnostic as if the skin biopsy were obtained elsewhere, and this was more or less disregarded.

This case is reported to point out the not infrequent finding of a simultaneous insult to the liver by a combination of disease processes, and if one were to retrospectively examine the protocol, the initial episode of hepatitis, quite severe, might have suggested that to us, and perhaps this obtains more often than we might expect. The examples of other combinations of diseases would be congenital hemolytic jaundice with cholelithiasis, the occasional and very rare combination of viral hepatitis treated with transfusions followed in turn by homologous serum hepatitis, cirrhosis with congestive heart failure, not too uncommon in the elderly patient, cirrhosis with hepatoma, and hepatitis occurring in a pregnant woman with toxemia of pregnancy. Another example would be cholecystic disease with subsequent obstructive biliary cirrhosis.

A review of the patient's case history indicated that an enlarged liver and normal liver function tests had been noted prior to the onset of hepatitis. This is not unusual in hemochromatosis, and since we are well aware that the defect in these patients is present much in advance of clinical awareness of the disease, no doubt the original viral hepatitis was certainly a severe insult. Surgery in this patient would have been a formidable stress, and it certainly points out again the importance of observation of the patient with jaundice and with hepatitis, at least for a period of time during which the clinical features and laboratory features become more typical.

Case 3:—This is a 20-year old Negro male who presented an extremely difficult diagnostic dilemma. The initial history consisted of rather severe epigastric pain with nausea, vomiting, chills and fever noted for a two-week period of time during which a weight loss of 22 pounds was sustained.

Physical examination revealed tenderness with rebound in the upper epigastrium. Leucocytosis was evident (W.B.C., 15,400). Serum amylase determination was 870. The urinary diastase was 1,000 units. Alkaline phophatase was 26.7 Bodansky units. An upper gastrointestinal examination was negative. Two days later the amylase had returned to an almost normal level of 195.

He was dismissed for a two-week period of time after two weeks' hospitalization, and was readmitted three weeks later with a recurrence of his pain and vomiting. An additional weight loss of ten pounds was reported.

Laboratory data: W.B.C., 12,000; Serum bilirubin, 3.7; Total alkaline phosphatase was 35 units (Bodansky). The hepatocellular tests were within the range of normal. Amylase was repeated and found to be 860. Cholecystogram revealed nonvisualization.

The patient was observed for a two-week period of time during which the serum alkaline phosphatase remained peristently elevated as did the serum bilirubin. A transaminase of 300 units SGOT was obtained. At this point duodenal drainage revealed no crystals but gross blood was found.

At exploratory laparotomy the following was discovered:

(Slide) This is a papillary adenocarcinoma of the papilla of Vater, and again demonstrates how difficult this diagnosis can be. Dr. Schiff has pointed out in his monograph on the clinical approach to jaundice that this particular lesion may present as cirrhosis to the clinician, as ulcer disease with deformity of the second part of the duodenum. We may thus add to this list carcinoma of the ampulla of Vater presenting as recurrent acute pancreatitis. It was our feeling preoperatively that this patient had cholecystic disease with extrahepatic biliary obstruction and secondary pancreatitis.

Case 4:—A 36-year old male in whom examination revealed scleral icterus and a palpable liver. The liver function tests were all normal with the exception of the BSP which revealed 20 per cent retention after 30 minutes.

A diagnosis of hepatitis was established.

During the next three years intermittent icterus, particularly with stress, was noted. Cholecystogram revealed faint visualization of the gallbladder. Liver biopsy.

(Slide) This is a beautiful slide showing the characteristic coarse granules in the hepatic cells. The distribution of the pigment is central lobular, which is characteristic of the Dubin-Johnson syndrome. This particular defect, genetic defect, in bilirubin metabolism is one which has very difficult clinical aspects presenting a considerable problem to the clinicians who evaluate these patients. In a review of 50 patients Dr. Dubin pointed out that 31 laparotomies had been performed, and if one were to analyze the clinical data obtained in these cases,

that of intermittent jaundice and abdominal pain, dark urine, high direct serum bilirubin, normal hepatocellular liver function tests, and usually nonvisualization of the gallbladder, certainly this evidence would point to an obstructive form of jaundice.

The features which might help in making a proper diagnosis would be, first of all, an awareness that these different diseases exist and familial history obtained in a good proportion of the cases, and the value of analyzing the history with regard to intermittent icterus, as far as the precipitating factors of stress, infections, etc. So oftentimes these patients are labelled chronic hepatitis, that it is important from the standpoint of prognosis, which is good in the Dubin-Johnson snydome and in constitutional hepatic dysfunction and their variants, that the proper diagnosis be made. The value of the liver biopsy in the diagnosis of this latter case is paramount since the pigmentary lesions may be confused with other conditions in which pigment is present in the liver, it is important that the liver biopsies be studied by pathologists who are interested and experienced in the diagnosis of hepatic pathology.

PROBLEMS IN THE DIAGNOSIS OF ACUTE PORPHYRIA*

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Acute porphyria has received considerable emphasis as a consideration in the differential diagnosis of acute abdominal disorders. Its position in this respect is rightfully deserved. If the possibility of acute porphyria is at all in mind, the diagnosis of the classical case should offer little difficulty. Although most cases tend to develop certain features in common as the acute attack progresses, the presenting features are sometimes far from classical and occasionally quite bizarre. Ultimately the diagnosis of acute porphyria rests on the demonstration of an abnormality of pyrrole metabolism just as the diagnosis of diabetes mellitus is dependent on the demonstration of abnormal carbohydrate metabolism. Difficulties in the proper performance and proper interpretation of the laboratory tests designed to demonstrate abnormal pyrrole excretion are unfortunately common. It is the purpose of this presentation to call attention to some of the problems to be encountered in considering the diagnosis of acute porphyria.

Without doubt, the most prominent feature of acute porphyria is abdominal pain. Although virtually every case is eventually associated with abdominal pain this may not be the presenting symptom. Abnormal mental behavior may be the earliest recognizable feature of an attack. In these instances there are usually episodes of confusion and delirium, sometimes with severe agitation, occurring periodically over a few months or weeks and finally culminating in an acute attack with severe abdominal pain. A generalized convulsive seizure was the initial symptom in one of our patients, followed a few days later by abdominal pain. Convulsive seizures and episodes of syncope are not unusual complications of the acute active phase of the disease. On the other hand, although neurologic involvement with paralysis or paresis is a distinct hazard of the acute attack, motor disturbances are rarely a presenting symptom. One possible exception to this is hypotonicity of the urinary bladder with resulting urinary retention. This problem has been of sufficient severity to warrant cystoscopic examination in search for urologic pathology in some instances.

Much has been written about the abdominal pain of acute porphyria which is, in the majority of cases, the earliest symptom of the disease and the complaint

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which most often causes the patient to seek medical attention. Suffice it to say that the pain is usually severe, poorly localized, seldom accompanied by rigidity of the abdominal wall musculature and only transiently relieved by narcotics. Constipation is an almost constant feature of the acute attack and sometimes of the period just prior to its onset. Mild nausea occurs but vomiting is unusual. There are three ancillary features of the acute attack which are so constant that they merit special emphasis: tachycardia, hypertension, and pain in the extremities, especially in the thighs. In a young person suffering from acute abdominal pain, these findings should always alert the examiner to the possibility of acute porphyria.

We have the definite impression from our material that acute intermittent porphyria manifests itself, as the name implies, in distinct, acute attacks. During periods of remission the patient is usually quite well, the only interval symptoms being, occasionally, nervousness and some degree of emotional lability. Certainly the diagnosis of acute porphyria can seldom be documented in the patient whose problem is one of almost daily occurrences of abdominal pain over long periods of time.

There is a common misconception that the porphyrias generally are associated with photosensitivity. This is only true of porphyria *cutanea tarda* and congenital erythropoietic porphyria. Probably because only an insignificant amount of porphyrin *per se* is present in the serum in acute porphyria, light sensitivity does not occur.

One of the cardinal features of acute porphyria is the periodic excretion of a dark colored urine. This is usually associated with the acute attacks. This discoloration may vary from pink to "port-wine" color and sometimes is almost black, although when viewed against a strong light source even this urine has a reddish quality. The color of the urine is not entirely due to porphyrin *per se*, nevertheless there is a good correlation between the porphyrin content and the degree of discoloration of the urine.

Acute porphyria is characterized by the excessive formation and excretion of porphyrin precursors, in particular delta-amino levulinic acid and porphobilinogen, but not of preformed porphyrin. These chromogenic substances are colorless and nonfluorescent and are converted in the bladder (and tubular?) urine to porphyrin, principally uroporphyrin. The conversion to porphyrin is much more rapid at an acid than an alkaline pH. Thus the amount of porphyrin present in a specific urine sample will depend on a number of factors, such as how long the urine has remained in the bladder, or in a collection vessel, the pH of the urine, and other factors. It is apparent from this that all gradations of urine color and of porphyrin content can occur during active disease including the passage of a colorless urine containing virtually no porphyrin at the height of an attack.

What then are the biochemical requisites for the diagnosis of acute porphyria? It is our feeling that the demonstration of porphobilinogen in the urine is absolutely diagnostic of acute porphyria. Hence it is preferable to examine relatively freshly voided samples of urine. If more than 24 or 48 hours is to elapse before the urine can be analyzed, it is advisable to add a small amount of sodium carbonate and refrigerate the specimen.

The statement that the demonstration of porphobilinogen is specific for acute porphyria requires some qualification. The Watson-Schwartz[1] test for porphobilinogen is simple, rapid, inexpensive and an excellent method for demonstrating porphobilinogen in the urine. We have, however, encountered distinctly false positive results on occasion. More often than not we have been unable to determine the substances responsible for this type of reaction. The presence of melanogen in cases of melanosarcoma can result in a false positive test as will urine from patients taking Pyridium® although the latter produces a more orange than pink color. In urines containing large excesses of urobilinogen, not infrequently, a small fraction of the aldehyde complex cannot be extracted into chloroform even with repeated attempts. Because of these and other problems of interpretation, we have found it helpful to routinely apply the following confirmatory procedures to every positive result by the Watson-Schwartz test.

1. The aldehyde complex of porphobilinogen is insoluble in n-butyl alcohol. Some of the pink, chloroform insoluble supernatant from the Watson-Schwartz test is decanted and shaken with an equal volume of n-butyl alcohol and the solubility of the aldehyde complex noted. In almost all of the falsely positive tests encountered the aldehyde complex has been completely soluble in n-butyl alcohol.

2. Paper chromatographic identification of porphobilinogen. A few drops of urine are added to a strip of Whatman No. 1 filter paper. Using a developing solvent of butanol, acetic acid and water (80:5:15) an ascending chromatogram is run for approximately 2 hours in a closed chamber. The strip is dried in air then sprayed with Ehrlich's aldehyde reagent. The Rf value for porphobilinogen in this system is approximately 0.21 and clearly distinct from that of urobilinogen (0.35).

3. Demonstration of the formation of porphyrin from porphobilinogen. The porphyrin present in 10-15 ml. of urine is removed by adsorption on a calcium phosphate precipitate. The supernatant solution is adjusted to a pH of 3.5 and heated in a boiling water bath for 30 minutes. If the original urine contained true porphobilinogen, examination of the supernate will now reveal uroporphyrin, formed during the period of heating.

We feel that confirmation by one or more of these procedures should be obtained before the validity of the Watson-Schwartz test for porphobilinogen can be assumed.

If, in a urine specimen which has been standing for a few days, no porphobilinogen can be demonstrated but a large amount of uroporphyrin is found, the diagnosis is most likely porphyria. Two points must, however, be emphasized. One, small increases in urinary uroporphyrin can occur in disorders other than porphyria. Secondly, the finding of a large excess of coproporphyrin in the urine, but no increase in uroporphyrin, is not diagnostic of, or even consistent with the diagnosis of, acute porphyria. Certain disorders such as lead poisoning, liver disease and hemolytic states may result in an increased coproporphyin excretion in the urine. This, however, is nonspecific porphyrinuria and should not be confused with the disease entity of porphyria.

During attacks of acute porphyria the fecal porphyrin excretion is usually greatly increased. This increase is principally of fecal protoporphyrin and coproporphyrin but a distinct, although less marked increase of fecal uroporphyrin also occurs. With remission of the acute attack, fecal porphyrin excretion slowly falls and usually becomes entirely normal within a few weeks after the acute episode. Concomitantly, there is a fall in urine porphobilinogen and porphyrin excretion. Only very rarely, however, does porphobilinogen completely disappear from the urine. As a rule there is a continuous excretion of porphobilinogen in the urine in an amount readily detected by the Watson-Schwartz test. Thus, when urine is carefully examined for porphobilinogen by use of the aforementioned technics, the diagnosis of acute porphyria can usually be made even during periods of remission. It must be stated, however, that in rare instances all abnormal pyrrole excretion ceases between the acute attacks.

Both acute porphyria and porphyria *cutanea tarda* belong to that category termed "hepatic porphyria"[2]. This distinction from congenital "erythropoietic" porphyria is based on the abnormal porphyrin and/or porphobilinogen content of the liver in the former. Jaundice is extremely rare and most tests of liver function are normal in acute porphyria, even at the height of an acute attack.

An exception to this is the excretion of bromsulfalein (BSP). A fairly constant feature of the acute attack is the abnormal retention of bromsulfalein. Furthermore, a return to normal BSP retention is almost invariably accompanied by distinct clinical improvement even though porphobilinogen excretion may remain very high. We have found this an excellent, readily available, prognostic tool. An additional clinical application is in the patient, previously known to have acute porphyria, who suffers an acute episode of abdominal pain. The demonstration of abnormal BSP retention in this instance would suggest that this was truly an attack of acute porphyria and not an acute abdominal disorder requiring surgical intervention.

If one will keep these clinical features in mind: abdominal pain, pain in the extremities, hypertension, tachycardia, hysterical behavior, abnormal BSP retention and dark urine, overt acute porphyria will seldom escape detection. Nevertheless, it is felt that a diagnosis of acute porphyria based entirely on

clinical grounds is not acceptable and that it is mandatory that specific abnormalities of pyrrole excretion be demonstrated.

Summary

Some of the less common presenting features of acute porphyria are reviewed. The clinical biochemical aspects are discussed from the standpoint of proper interpretation and most useful application.

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Discussion

Dr. Julius Bauer:—Well, gentlemen, you have heard several very interesting papers. As far as the first most valuable paper of Dr. Field is concerned there is, of course, nothing to be added to what he told you. But I would emphasize another thing which I always miss in the instruction of young doctors and students.

There are cases, desperate cases of patients who are going to die anyway, and what is extremely difficult to teach is that such a case requires an individual decision: should he be allowed to die in peace without bothering too much? It is sometimes wiser to let him die in peace instead of tormenting him with all kinds of tests if you know that he is lost anyway.

That doesn't argue against the use of those substances which prove to be valuable in certain cases, but one has to individualize.

As far as the differential diagnosis of jaundice is concerned, the paper of Dr. Wallace, I think there is not much to be said. It was extremely interesting, particularly the last case presented and the previous case, the Dubin's type of jaundice. I think one mistake which you find in the literature often is that this Dubin's disease is identified with nonhemolytic hereditary jaundice, which is something entirely different from what is generally described as congenital, constitutional, or familial nonhemolytic jaundice, which is actually not a disease; as Gilbert and Lereboulet said, the patient is more yellow than sick.

As to the third paper, the very scientific paper by Dr. Redeker, in which he gave a lot of information, I want to mention one case which may be particularly instructive for practice.

Long years ago when I came in the morning to my service and asked the boys "What's new?", as I did every day, they said, "Well, at night a woman was

brought in with terrific pain, abdominal pain, acute pain, and we didn't find anything. We thought there was something in the genital organs. We called a Gyn. consultant and he found a twisted ovarian cyst. The patient is already transferred to the Gyn. service and the surgeons are already scrubbing to operate."

It was customary, which is not customary now any more, to collect the 24-hour urine of a patient always, and the urine was still in a jar just at the bed of the patient. I looked at this urine. The urine looked extremely dark to me. I said, "What's that?"

"Well, I don't know," they said.

I advised that they stop the surgeons for a moment and look for porphyria, and there it was. It was an acute porphyria.

This woman recovered from the acute attack, but within about six weeks she died from a not uncommon event, from an ascending paralysis of the Landry type, and the autopsy revealed that there was an ovarian cyst, but it was not twisted.

You see, it can happen that you have to deal with a porphyria where a physical examination gives you, or may give you, some clue as to the diagnosis, and the diagnosis may be wrong.

The last point I would like to mention is the differential diagnosis between porphyria and some type of psychoneurosis, which, as Dr. Redeker mentioned in the first case, is not quite uncommon. But what I used to miss in the routine histories of my boys is psychoanamnesis, if I may call it that. They take a very thorough history, routine, standardized, including chicken pox of the grandma or something of this kind. But a much more important thing to investigate is, what kind of a person is that? In which environment has she been living? And what is on her mind which might elucidate the case?

That is what I very frequently miss, and I think it is absolutely wrong to make a diagnosis of neurosis or psychoneurosis just because we can rule out any tangible organic disease. We must also find a positive clue for the diagnosis of psychoneurosis. You don't need a psychiatrist for that. You have to do it yourself. Every internist, every general practitioner, must know that. And if we internists see about 30 per cent of our patients as a general experience who are pure and simple psychoneuroses, and if we see 30 more per cent of cases where an organic disease shows an overlay with psychoneurosis, then it is our duty to investigate ourselves. There is no good coming from transferring such patients to psychiatrists because the psychiatrist has other problems to solve, and there are too few of them. I don't say more about that, but I think it is the duty of the internist to investigate also the emotional life, I don't say in everybody, but where it seems to be a point of importance in the differential diagnosis.

Dr. Clarence J. Berne:—I think that it is interesting that these cases, at least the last two, dealt with problems in which there were combined situations, and this is, I think, part of Dr. Bauer's discussion, that it is traditional to teach students to always try and make one diagnosis to fit all the patient's problems, and that you tend to err if you stray from this basic principle.

I am reminded of what Dr. Zinsser said with regard to the question, "What is it that has four legs and flies?", and the answer is "Two birds," and that very often in the situations that have been mentioned here—in Dr. Wallace's, and I am sure that one could raise the question with Dr. Redeker—that people with porphyria are not immune to other maladies within their abdomen, and the fact that a person is porphyric doesn't always settle all the questions.

I am fascinated with Dr. Bauer's observations on the chromatics of the urine jug. I don't want to beat you on this, Dr. Bauer, but I once saw this on a man sick in the hospital, with a nice white hospital gown on, who came out of the toilet and went back to bed with his doctor standing there. He had a red patch on the front of his gown which was erroneously thought to be some red ink or mercurochrome or maybe a little blood or something, but wasn't realized to be the nice red urine of porphyria. So there are at least times when a diagnostic observation could be made and it stares you in the face and you see it and don't realize it.

I think it might be interesting if Dr. Redeker were to answer a question as to what causes acute abdominal pain in porphyria, and maybe he might have a moment to say something about the interesting phase regarding the need to avoid use of barbiturates.

I think that the problem of diagnosis in the acute abdomen in a patient with porphyria that is not known to exist is like the diagnosis of many other such strange, difficult problems—sicklemic crises and hysterical proptosis and so forth. Where there are very few objective data that will establish the diagnosis in the middle of the night any diagnostic help is doubly important and leads from which one can expect this help are things that are always worthwhile being told about.

I, for one, enjoyed very much Dr. Field's presentation. While Dr. Field is an authority on such matters, I, like most of us here, am fascinated to hear of the progress that is being made. It has been my observation, from listening to authorities in these fields talk about recognition of the importance of 5-fluorouracil that many people are extremely thrilled over this chemotherapeutic breakthrough which is actually thought to be a long step forward in the creation of substances which constitute cytotoxic therapeutic agents.

The concept of their use as adjuvant therapy in the operative management of cancer, particularly of the stomach and colon, establishes the basic principle

that the surgeon's problems and his hypotheses and concepts regarding what he is doing when he operates upon a colon carcinoma have been importantly extended by fuller realization of the potential danger from shed cancer cells. These cells, which can be transplanted lie in the lumen of the bowel at distances well below the lesion. Also, serosal breakthrough of the primary tumor may exist without this being visible, and the gutters and other areas in the abdomen may contain shed cells. From the opening of the bowel itself, in the area where the resection is done, transplantations can occur by spillage of bowel mucus containing shed cells into the peritoneal cavity, into the wound, and so forth.

In a way this isn't difficult to visualize. It's like the early concepts regarding bacteriology in relation to surgery. Lister spent years making people understand what was going on with microbes that they couldn't see, and this same thing is now at hand in cancer surgery. This is a concept which has to evolve, and technics and agents have to be developed for use in the operating room to deal with these transplantation problems.

I think great steps are being made in this field. Even in the basic technic of surgery, regardless of the use of cytotoxic agents, at the time of surgery surgeons are modifying and learning much in the way of altering what is done in the operating room, based on the concepts of shed single cells and clumps.

So I think now that we will go to asking for questions from the floor, and we would appreciate very much any questions to Dr. Field, Dr. Wallace, or Dr. Redeker.

Question:—I wonder if Dr. Bauer has any comments to make on jaundice from the use of testosterone.

Dr. Bauer:—Well, I think it is only methyltestosterone which may occasionally produce jaundice, which is of a similar type to that after chlorpromazine, but personally I have no experience with it. I have never prescribed any methyltestosterone. If I need testosterone it is better to give it in injection form. It's safer.

Dr. Allan G. Redeker:—You have posed two questions, Dr. Berne. One question is the cause of abdominal pain. I think no one has any real ideas of the cause, but I think sufficient investigative work has been done to eliminate porphobilinogen or the porphyrins as the causative agents in abdominal pain. The cause must be something other than these compounds.

There was one other question that I can't recall.

Dr. Berne:—If you wish to, we will give you a moment to comment about the barbiturates.

Dr. Redeker:—Of course they are quite contraindicated. I might refer back to the last slide I showed, of the 27-year old boy, who very briefly, suffered this

problem: He received an amount of barbiturates commonly administered during this type of surgery, went home on the fourth day; the night of the fifth postoperative day he was readmitted to the hospital with severe abdominal pain. It would be hard to believe that the surgery itself was solely responsible and that, at least potentially, the barbiturate had nothing to do with the onset of the disease postoperatively.

Dr. Bauer:—I want to comment on the mechanism of the abdominal pain. I don't think we have to give another explanation for the pain which you see, for instance, in Addison's disease, or in Simmonds' disease, where people occasionally have severe abdominal pain, and just in the last two or three years some anatomical changes were described in porphyria in the sympathetic ganglia; we don't know very much about the clinical importance of the sympathetic ganglia at all.

I used to say, "Well, you have to know about the solar plexus just for the examination in anatomy and maybe also in physiology and pharmacology, but not in internal medicine." Who knows something about a disease of the sympathetic ganglia? I think that it is very probable that these pains, these abdominal crises, are actually not well explained.

You saw in former days in more advanced cases, an unusual number of crises in tabes, which we don't see any more these days. Today this is almost an obsolete disease, at least here in California.

The mechanism of these crises is probably also by reason of some functional disturbance in the sympathetic ganglia, whether it is in the solar plexus or somewhere else. But as far as porphyria is concerned, some anatomical changes have actually been found.

Question:—I would like to hear some comment about the use of steroids in conjunction with viral hepatitis and the results obtained.

Dr. Bauer:—Well, I think there is no question that in certain instances steroids have a beneficial effect on these cases of hepatitis, but it is hard to say which case will respond and which will not respond. I remember a case where ACTH had a good effect and cortisone before that had no effect at all. It is very difficult to evaluate the effect of these steroids, particularly when we know the very variable course of hepatitis without any treatment.

Dr. Berne:—Dr. Wallace, do you care to add to the answer to this question?

Dr. Alexander Wallace, III:—A thorough clinical evaluation by the Nelson Sprinz Group of the Hepatitis Center in Europe indicated that in the average case of hepatitis, steroids were not particularly efficacious. In the majority of cases studied, the course and severity of the disease was not significantly affected as compared to the untreated patients. There was little evidence to indicate

enhancement of immunity, and in fact, a high relapse rate was noted in the steroid treated patients. The general consensus now is that steroids are rather disappointing in effect and are perhaps best utilized in those acute fulminating forms of hepatitis where ordinary therapy is unavailing. It is my feeling that since the introduction of newer steroid drugs, which possess considerably less side-effects, that additional trials of these newer compounds perhaps in higher dosages may prove to be more effective.

THE GASTROINTESTINAL TRACT AS THE TARGET OF NEUROLOGIC DISEASE*

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Gastroenterology and neurology converge in certain syndromes. There are patients with neurologic disease whose symptoms are manifested in apparent gastrointestinal disorder. There are patients with gastrointestinal disease who present with neurological findings. And finally there are patients whose disease is reflected in both the gastrointestinal and nervous systems.

The first group, patients whose neurologic disturbance is masquerading within the abdomen, includes several conditions and complaints, perhaps the most disturbing of which to the patient is that of pain. The pain may be radicular or cramplike depending upon the source.

Radicular pain develops when the posterior roots of the spinal cord are impinged upon or diseased. Diagnosis of a neurological disorder usually can be made from the description of the pain. It is sharp, lancinating, shooting, and occurs usually within the distribution of one or two roots. Radicular pain rarely is felt as piercing through the trunk but instead as radiating around or partly around in an area about the width of a belt.

Radicular pain tends to be intermittent and to be relieved by deep pressure. In cases of tumor within the vertebral column, however, it may be continuous. It is somewhat relieved by aspirin, and is aggravated by coughing, sneezing or straining.

Diagnosis of the cause of the radicular pain depends upon the examination of the patient and the roentgenological findings. If the tumor is located adjoining the spinal cord, the patient has sphincter disturbance, weakness of one or both legs, more-or-less of a sensory deficit, and will probably have been seized by a neurologist before getting to you. If, however, the tumor is a neurofibroma involving just a posterior root, examination reveals only hypalgesia or hyperalgesia in the distribution of the root, and exaggeration of pain by one or all of three maneuvers: sharp flexion of the neck, straight leg raising and by bilateral jugular compression. A neurofibroma of the posterior root may cause erosion of the spine but this cannot be demonstrated by anterior-posterior or lateral x-rays. It is necessary to take an oblique view of the facets.

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Herniated disc or compression fracture of the spine occurs rarely in the thoracic area. When either does, the pain is referred to the abdomen, and may be the solitary finding. In these instances, however, roentgenograms are definitive, and electromyogram may depict associated anterior root pathology.

Chronic arachnoiditis mimics spinal cord tumors, appears at any level, and similarly gives rise to radicular pain. The pain usually is more widespread than that of tumor and less characteristic which makes diagnosis difficult; but fortunately for the doctor, the neurologic findings are more apparent. Roentgenograms prove nothing.

Certain diseases characteristically affect the posterior roots giving rise to pain. Herpes zoster is an infection related to chicken pox. It is common in older people. The onset is with severe burning pain in the distribution of one or two roots on one side. Palpation reveals both superficial and deep tenderness at the site of the pain. The skin lesion usually develops within one or two days, but sometimes may be delayed. In these cases hyperalgesia, increased sensitivity to pin prick, in the distribution of the affected roots is the only diagnostic criterion.

Radicular pain may be incident to pernicious anemia, diabetes, Hodgkin's disease and most common of all *tabes dorsalis*. In *tabes dorsalis* the pathology usually begins distally in the spinal cord. Therefore patients give a history of similar pains in the legs, an uncommon site for pain of gastric origin, for years preceding the pain in the abdomen.

Gastric crises are the nightmare of both patient and doctor, at least in treatment. Possibly the gastroenterologist does better than the neurologist in helping his patients. The diagnosis is made from: 1. History of repeated episodes of vomiting with or without cramps, but with no abdominal discomfort or symptoms between episodes. 2. A past history of syphilis and of lancinating pains in the legs. 3. The typical findings of *tabes dorsalis:* Argyll Robertson pupils; absent patellar and Achilles deep tendon reflexes; absent position sense and vibration sense in the feet; decreased muscle tone with pathologic limberness; and urinary incontinence associated with a distended bladder. More often than not the neurologic findings will be incomplete. Positive serological reactions are confirmative; but negative responses do not exclude the diagnosis of *tabes dorsalis*.

Cramping pain in the abdomen and vomiting may be caused by porphyria and abdominal epilepsy.

The malignant type of porphyria is a poorly understood familial metabolic disorder, characterized by excretion of porphyrins in the urine, some of which cause the urine to turn dark when exposed to light. It begins during the third decade of life with episodes of vomiting associated with acute abdominal pain and tenderness. At first the neurologic examination may be noninformative. Later patients develop a peripheral polyneuritis, manifested by impaired touch,

pain and vibration sense in the feet, and absent Achilles reflexes. As time goes on, patients become acutely ill, and develop seizures, mental disturbance and progressive weakness of the feet and legs from extension of the peripheral polyneuritis. The finding of porphyrins (uroporphyrin, leukoporphyrin, hematoporphyrin) in the urine clinches the diagnosis.

Abdominal epilepsy is as benign as porphyria is malignant. Patients usually have a history of epilepsy; but otherwise they have no symptoms in between attacks. There are no findings on neurologic examination. Palpation of the abdomen does not, however, elicit either rebound phenomenon or much tenderness. If it does, differentiation from an acute surgical abdomen hangs precariously on the blood count. Episodes are not helped at the time but are reduced in frequency by anticonvulsant medication.

Vomiting without abdominal pain may be produced by neurologic disease. Brain tumor is the most serious and unfortunately, the most common cause. The vomiting is due to irritation of the vestibular apparatus or of the medullary center. In the latter instance it occurs chiefly in those cases with increased intracranial pressure due to malignant glioma. Patients with brain tumor complain of headache, which is not too severe and which is somewhat relieved by aspirin. They do not lose weight. They are not anemic and they have no other symptoms. The abdomen is soft and nontender. The neurologic examination may reveal nothing except papilledema.

The vomiting associated with vestibular disease is precipitated by change in the position of the patient. The doctor who suddenly moves such a patient's head is likely to be showered with vomitus, an accurate but unesthetic diagnostic procedure. Patients usually have a marked nystagmus, symptoms referable to the ear and possibly some dysmetria of the ipsilateral limbs.

Patients in the last group whose neurologic pathology leads them to the internist manifest acute ulceration or more often hemorrhage from the upper gastrointestinal tract.

The cerebral pathology in these instances may be of practically any type: Spontaneous intracerebral hemorrhage, spontaneous subarachnoid hemorrhage, brain tumor, head injury, poliomyelitis, encephalitis, cerebral infarction, meningitis, cerebellar cyst, choreoathetosis, frontal lobotomy and pneumoencephalography have all been reported as causing gastric bleeding. The cerebral lesion may be located at almost any site in the brain. The cerebral insult is usually severe.

When the vomiting of blood precedes the cerebral insult, diagnosis of the neurologic disorder is practically impossible; more often, the gastrointestinal symptoms follow the neurologic. In almost all, the patient is seriously ill.

In the cases of tumor, the gastric symptoms usually occur after some sudden change, such as spontaneous hemorrhage within the tumor, acute worsening of the patient's condition or following surgery.

In general neurologically induced gastric hemorrhages or ulcers are multiple, minute and acute. Rarely does a brain tumor cause a chronic ulcer.

The next group of cases to be discussed is that in which the gastrointestinal disturbance is cloaked behind a neurologic deficit.

Posteriorly placed peptic ulcers provoke pain in the back; and, although this pain is relieved by a bland diet, it is the rare patient that detects the correlation. Similarly peptic ulcers may cause radicular pain in the thoracic or abdominal area. Since the pain is so typically radicular—a lancinating, shooting pain, referred to the skin or external tissues, peptic ulcer is not considered, and the patient is studied from the neurologic standpoint instead.

Any debilitating or wasting disease or any disease associated with increased metabolic demands may cause a peripheral polyneuritis. A malignant neoplasm of the gastrointestinal tract may present, so far as the patient's complaints are concerned, as a numbness, tingling or burning of the feet. Typically, examination reveals only impaired two-point discrimination, touch and vibration sense and either a hypo- or hyperalgesia of both feet. The Achilles deep tendon reflexes are diminished or absent. Often the sensory findings are incomplete. Diseases or infections of the gastrointestinal tract preventing the absorption of Vitamin B likewise may become apparent first as a peripheral polyneuritis. In all of these, the patient may complain primarily of paresthesias of the soles of the feet. As the neuropathy becomes worse, the symptoms extend up the legs, but the patient still may have no complaint referable to the underlying pathology. Possibly the discerning gastroenterologist should proceed directly from the feet to the abdomen, and spare his patient the detour through a neurologist.

Lastly there are a number of diseases which engender symptoms in both the gastrointestinal and nervous systems. These include pernicious anemia, diabetes, thyroid dysfunction, avitaminosis, alcoholism, syphilis, tuberculosis, parasite infestation and a legion of others which are beyond the scope of this paper.

In conclusion, the nervous system sends its tendrils to all parts of the body. It is not surprising therefore that its pathology is reflected in disturbance elsewhere; and that, similarly, gastrointestinal disease may incite a nervous system response. It is not surprising, but in some cases it greatly enhances the doctor's problem in reaching the correct diagnosis.

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PSYCHOLOGICAL ASPECTS OF ULCERATIVE COLITIS*

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Ulcerative colitis is a disturbance of great complexity. The participation of allergist, internist, proctologist in the present discussion attests to the diversity of considerations involved in an approach to an understanding of the illness. My task is to report upon the psychological observations of patients suffering with ulcerative colitis and, if possible, to indicate their relationship to the general clinical disturbance.

The psychological study of patients with ulcerative colitis has been rather intensively pursued. Among the early efforts to investigate the significance of psychological factors in gastrointestinal illness was that of Alexander[1] who, at that time, attempted in preliminary fashion to compare the predominant conflict-situations, and the patients' attempts at solutions of them, in gastric cases, in diarrhea and in constipation. This ushered in the many years of investigation of the specific nature of conflict situations in psychosomatic disturbances by Alexander and his colleagues, at the Chicago Institute for Psychoanalysis, recently and currently being reported[2].

In these studies, the approach is not an etiological one, but rather an attempt to verify clinically suggested and hypothesized correlations, between organic symptoms and psychological patterns. The presence of an unknown constitutionally predisposing factor is assumed; without this factor presumably the presence of psychological conflictful situations characteristic for given psychosomatic illnesses would not necessarily determine the presence of the illness. On the basis of clinical observations, it is further suggested that a third factor is operative in the actual precipitation of the symptoms of illness, e.g., a difficult current life-situation or specific event that mobilizes affect stemming from the central conflict situation. This hypothetical position has found support in studies such as that of Mirsky[3] who has convincingly demonstrated the greater susceptibility to duodenal ulcer in individuals with gastric hypersecretion. Mirsky's observations indicate the possibility of predicting the likelihood of occurrence of duodenal ulcer under given conditions. Murray[4], Sullivan[5], Brown[6], Wittkower[7], and Daniels[8] made early contributions to the clinical studies.

The numerous studies of adult ulcerative colitis patients in recent years has been supplemented by investigations of the condition in children. Mellita Sperling[9,10,11] in particular has psychoanalytically studied and treated children, and has demonstrated the dynamics involved in understanding symptomology

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in terms of emotionally conflictful states with which the patients must cope. Mohr[12], Josselyn[13,14] and the group who have been studying psychosomatically ill children at the University of Illinois Department of Psychiatry, have furthered these investigations. Engel[15] has most exhaustively reviewed the literature, has discussed the illness as one in which intestinal ulceration represents a late manifestation in a general disturbance in which bleeding and constipation are earlier symptoms, and has emphasized the significance of the patient's separation from a crucial personality as a precipitating factor.

The studies of Alexander and his colleagues indicated rather characteristic features in the patient's life situation, and in a central conflictful state. Quite consistently, ulcerative colitis patients prove to be people who have suffered severe disappointments in their efforts to achieve their goals. Time and again, one hears of ineffective efforts to accomplish their purposes; work careers are frequently characterized by numerous job changes and indications of poor capacity to follow through in the face of real demands. Not infrequently, a history of consistent or long-time employment on a given job proves to be a continuing attachment to a non-demanding job situation in a protective setting, e.g., employment in a family business. The patient is inclined to defend his status by emphasizing the high quality of his performance in the particular work setting, and to indicate how essential his presence and performance are, e.g., "I work slowly, but do a much better job than others do in a situation such as this." The patient actually is in a quite dependent position, needful of the protection offered him, but unable to accept or acknowledge his dependency. This operates in an atmosphere of great anxiety and mistrust on the patient's part of his actual ability to meet the demands made upon him. Investigators have repeatedly emphasized the attitudes of helplessness and hopelessness that characterize the ulcerative colitis patient. He has no convictions about his ability to accomplish his purposes, and struggles desperately with a feeling of constantly impending failure. New or more mature environmental demands that confront the patient are reacted to with characteristic anxiety about his ability to meet the new situation; symptoms may be exacerbated at such times. The need for continuing support from protective parental representatives is great; denial or frustration in this respect is reacted to unfavorably. A college student who had made a good recovery from a rather severe bout of bloody diarrhea, temporarily relapsed when the dietitian in the eating club he attended was a bit refractory in meeting some of his dietary demands; after a somewhat unpleasant exchange with her about his needs he again developed symptoms.

The ulcerative colitis patient gives a history of rather unsatisfactory experience with respect to the maternal care he has received. The histories reveal maternal ineffectiveness, indifference or other indications of lack of capacity to provide for the care of a child. Psychoanalytic studies of adult patients affirm the anxious, hostile interchange between the patient and parents, particularly the mother.

A more definitive approach to a clarification of early life-considerations that have bearing upon the occurrence of ulcerative colitis has been provided by the studies of children suffering with the disease. Sperling's[9] psychoanalytic studies are particularly impressive. Mothers of the children studied were found to be highly ambivalent and subjected the children to early and deep frustration. They showed unconscious destructive impulses toward the child, with a wish to be rid of the burden of its care. This evokes in the child a strong, hostile, dependent attachment. Our later studies[12] of hospitalized children suffering with ulcerative colitis are in keeping with Sperling's observations. The background for the ineffective and destructive unconscious attitudes of the mothers lies in their own unhappy experiences with respect to care by their own cold, severe, domineering and controlling mothers. They themselves had experienced a lack of maternal warmth and care, and had failed to win maternal love and affection despite serious effort to do so. Great dependent need in relation to their mothers, never gratified, is masked by a defensive pattern of self-sufficiency. In turn, these mothers betray patterns not unlike that of their own mothers, in dealing with the child ill with ulcerative colitis. They too are domineering and controlling. But the motivation for this effort at control is a deep fear that failure will have disastrous consequences. Actually these mothers do poorly in providing for the emotional needs of the child, and react with anxiety and with great sense of failure and discouragement. The child's illness is felt to be a confirmation of their own inadequacy. It is likely that the actual biological security of the child is very early threatened by the mother's inability to provide care. Josselyn[13] stresses indications that the earliest care of the child is made particularly difficult for the mother by external events that lessen her ability to provide for the child, because of emotional depletion and decreased available energy. Pregnancy and the demands of the early care of the child are experienced as undesirable and damaging, rather than gratifying, by the mothers. The attitudes of the fathers at times are quite significant; some fathers are supportive to the mothers, others undermine their already impaired resources as mothers. In one instance the destructive behavior of the father was considered highly determinative of the mother's inability to meet the demands of the additional pregnancy resulting in the birth of the ill child.

In view of the great limitations the mothers manifest, and the anxiety and hostility with which they approach the probems of care of the child, it is clear that the child suffering with ulcerative colitis is enveloped in a stressful situation that evokes both anxiety and hostility in him. The child as well as the mother is concerned as to basic biological security. The mother is experienced by the child as an undependable source of comfort and security. Fantasies about the incompetent and destructive nature of the mother are frequent, and may be expressed in fantasies about the dangerous or poisonous nature of the food that she provides for him. The initial feeling of lack of confidence about what the mother can

provide is extended to include all persons and situations involved in his care. The ulcerative colitis patient lives in an atmosphere of mistrust and great anxiety in a hostile world that fails to meet his needs and that threatens his existence.

The child's response to this situation that threatens to overwhelm him is an attempt: 1. to evoke from parents the care he needs through regressive infantile demand and 2. to become self-sufficient and himself solve the problems and meet the needs with which the parents are unable to cope. The former reaction is in keeping with the general resistance to demands made by developmental and maturational changes common to childhood. The augmented anxiety evoked by the concept of the dangerous nature of more mature life leads to a clinging to the more infantile position of dependency upon parental attention and care. Since these children already have suffered disappointment in this respect, the demand is urgent, hostile and primitive in nature. It is reflected in clinging to patterns of illness, in avoiding experiences that separate the child from the parents, at times in resistance to school attendance. Josselyn[13] has called attention to actual academic learning disturbances that are related to this need to avoid involvement in the requirements of more mature levels of functioning.

The other general response to the child's feeling or awareness that his parents have been unable to provide for him in a manner that assures a sense of security, is to undertake to do for himself that which the parents have been unable to do for him. He makes an effort to control his environment in a manner that will assure him the care he needs, and he attempts to solve the problems that his parents have been unable to solve. His mistrust of the ability of the adults about him to provide adequately for him is justified in that the anxieties of the parents about their own ability to function is communicated to him. Practical problems involving housing needs, employment, medical care, other familial needs, properly the concern of the parents, become anxious preoccupations of the child, who may be active in attempting to meet the need and prolific in his recommendations, suggestions, demands directed toward meeting them. Among the hospitalized children, this spills over into the area of hospital and medical care, about which a bit more will be said later.

With adult patients, an anxious overstriving, with lack of conviction that success is possible, is a characteristic finding. The college student struggling to attain a degree in which he feels inadequate to the task, or the worker struggling with the demands of a situation he feels to be beyond him, are common examples. One source of his discomfort is that he will disappoint the expectations of those on whom he depends and whose sustaining love and emotional support he ardently desires. It has been observed that parents have too great expectations of the ulcerative colitis patient, so that his efforts are initially handicapped by what he feels to be the discrepancy between his abilities and the demands upon him. I am of the conviction, however, that this is more a matter in which the initial threat comes from the incapacity of the parents to vouchsafe security; the

initial lack of conviction about the ability to meet life demands are those of the parent. This attitude can be internalized by the child, as can any principal basic attitude of parents, through processes involving introjection and identifications. Against this background is the effort of the child to solve the dilemma for himself by assuming responsibility for the solutions the parents have been unable to achieve. This is the more immediate order of too great expectations of the child; that is, those involving the felt necessity to meet problems that really are beyond him. Failure has the connotation of death or destruction, just as the initial failure of the parents implies a threat to survival. The characteristic reactions of helplessness and hopelessness, common to patients with ulcerative colitis, are noted at a time when he can no longer defend himself from the sense of impending disaster through the defensive efforts at self-sufficiency.

The basic attitude of mistrust toward adults who have failed them is manifest at times in the reactions of the hospitalized children. They make close attachments to the doctors and nurses who care for them. The hospital personnel at all levels can be helpful in functioning as dependable and reliable sources of help and support. Some of them will serve as scapegoats, toward whom the child directs the mistrust and hostility actually experienced in relation to the parents. But even with the evidences of interest and medical and nursing skill about him, the child at times will here too anxiously react to all efforts at aid, and in characteristic fashion, attempt to control and direct his own treatment. Children readily learn about the technical procedures, such as venoclysis, transfusion or other procedures. The child's reactions to these procedures will range from regarding them as potentially life-saving to being dangerous threats to his existence, just as he regards the mother's administrations inadequate or dangerous. These special reactions can be worked through in psychotherapy that is a part of the over all program of medical care.

Psychotherapy correlated with appropriate pediatric and other medical care may play a significant role in over all treatment of ulcerative colitis. Adolescent and adult patients can be helped to reveal the deeper sources of the basic pessimism, self-mistrust and tendency to give up in efforts at achievement characteristic for these patients. Insight into the nature of these emotionally significant reactions is part of the process that enables some patients to re-orient themselves emotionally and to advance toward more mature and more effective means for meeting their inner feelings and the practical demands of the environment. This generalization finds specific application as the patient discovers and copes with his hidden aggression toward his disappointing mother, his fantasies about her destructiveness toward him, his infantile demanding and dependent attitudes, his basic mistrust of his own powers.

The studies of children tend to place ulcerative colitis within the framework of a three-generational concept of psychological and psychosomatic illness. The manner in which emotional disturbances of the mother, as they involve primarily

her relationship to her own mother on the one hand, and as they are reflected in disturbances in her capacity to provide adequate mothering care to her child, is made clear in the studies of children with ulcerative colitis. Ideally, treatment would be prophylactic; very early help to mothers in the initial care of their children would tend to lessen the likelihood of occurrence of ulcerative colitis, as of many emotionally determined disturbances of childhood. Therapy for the mothers of children with ulcerative colitis is a part of a rational treatment plan that includes psychotherapy for the child. Immediate responses, as far as symptomatic change is concerned, at times may be dramatic[9], but the tendency toward remissions and recurrences often betrays the tenuousness of the symptomatic improvement attained. Actual restoration of the patient's freedom for development in keeping with maturationally determined potentialities is the basic goal of psychotherapeutic efforts. In childhood, collaborative effort of the pediatrican and child psychiatrist is frequently rewarding. The child in his family setting is here actively investigated with treatment directed toward the disturbance in the mother or parents as well as that of the child. With adolescents and adults, psychotherapeutic procedures are those usual in the treatment of neurotic disorders.

Experience with adults as well as the studies with children has strengthened the conviction that ulcerative colitis is an illness involving disturbance in neonatal experience that tends to impair normal emotional development. In a constitutionally predisposed individual, later environmental stress or unfavorable events precipitate intestinal bleeding through mechanisms as yet not understood. Despite the unknowns in this formulation, some of which are under active investigation at the hands of neurophysiologists, biochemists and endocrinologists, it serves to provide a perspective in which the clinical efforts of the various medical specialists involved in the actual care of the patient may be envisaged and rationally related one to the other.

Summary

1. Ulcerative colitis is a general disturbance in which intestinal bleeding and constipation are early symptoms, and in which intestinal ulceration is a late manifestation.

2. Like certain other psychosomatic disturbances, a constellation of factors operate in determining the illness. These include an hypothesized constitutional biological or predisiposing factor, the presence of a characteristic emotionally significant conflict situation, and the precipitating effect of unfavorable current events.

3. Normal emotional development has been impaired by unfavorable neonatal events.

4. Psychologically, ulcerative colitis is envisaged as a three-generational disturbance. The mothers of patients have suffered great deprivation in their

relationship with their own mothers and have never been able to win maternal love. They feel inadequate and ineffective in their own maternal role. The mother's anxiety and sense of inadequacy are transmitted to the child, who reacts with mistrust and hostility toward the disappointing mother who does not meet his needs. This mistrust extends to the environment; the child experiences the world as threatening and dangerous.

5. The child suffering with ulcerative colitis attempts to meet his situation by a compensatory effort at self-sufficiency. He himself undertakes to solve the problems he feels the parents fail to meet. This results in an overstriving in an attempt to avoid fantasied disaster.

6. When compensatory efforts threaten to fail, symptoms may be precipitated or exacerbated with characteristic associated feelings of helplessness and hopelessness.

7. Psychotherapy is directed toward restoration of the possibility of further emotional development and the achievement of ego strength permitting adequate solution of the disturbing problems of interpersonal relationships that hamper the individual.

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CHRONIC ULCERATIVE COLITIS—ATOPIC ALLERGY IN ITS ETIOLOGY*

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Clinical evidence from our 20-year study of chronic ulcerative colitis increasingly indicates that an eczematous-like allergic inflammation due to food and less frequently to pollen allergy is the probable cause. To Andresen[1] belongs the credit of recognition of such food allergy. We have amply confirmed its importance and in addition have recognized pollen allergy alone or associated with food allergy in the causation of chronic ulcerative colitis. We therefore concur with Andresen's recent statement that "almost invariably the cause of this disease is allergy." Our evidence published especially in 1942, 1948, 1950, 1954 and 1955[2] has been incorporated in a recent contribution[3] in which the histories, physical, laboratory and x-ray findings, the indicated allergic causes, results of treatment during cooperation in our antiallergic and adjunctive therapy in each of 170 cases treated in the last 20 years are summarized.

Though the characteristics of the disease favoring atopic allergy as the cause have been discussed in previous articles, their importance justifies their reiteration.

1. The frequency of gastrointestinal allergy†[4] is obvious with open-minded and adequate use of trial diets, especially with our fruit-free or our minimal elimination diets.

2. Allergic vasculitis and inflammation explains the erythema, the granularity, edema, friability, bleeding, oozing of sera, thrombosis, and resultant necroses, ulcers, fistulas and perforations with peritonitis.

3. Scar tissue and fibrosis with resultant contractures and strictures may arise from allergy alone with or without secondary infection.

4. Fever[5] may be due to allergy with or without secondary infection.

5. The colon and small bowel may be the only shock tissues of allergy. The family, personal and diet histories may reveal no apparent allergy.

6. Allergy may be localized in any part of the colon or small bowel, as is atopic eczema in the skin, especially on the face, flexures and hands.

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†Allergic diarrhea is often attributed to so-called idiopathic or nervous diarrhea.

7. As atopic dermatitis tends to spread so allergic inflammation may extend through the colon and small bowel.

8. Remissions occur in chronic ulcerative colitis as in other clinical allergy, such as asthma and eczema, due to refractoriness when the antibodies in shock tissues are temporarily exhausted or inactivated.

9. Activation of chronic ulcerative colitis occurs from transfusion of blood[6], especially plasma containing foods allergic to the patient (Wharton). Other clinical allergy may occur.

10. The relief obtained from antiallergic treatment alone in 49.4 per cent of our 170 cases and from corticoid and ACTH therapy by other students favors allergy in the causation of chronic ulcerative colitis.

Careful analysis of the causes in 170 cases of chronic ulcerative colitis[2] indicated by results from antiallergic study and therapy for 20 years up to 1958 are shown in Table I.

TABLE I

Food allergy alone	41.0%
Pollen allergy	2.9%
Food and pollen allergy	10.6%
Food and probable pollen allergy	15.0%
Pollen and probable food allergy	8.0%
Questionable food and pollen allergy	7.4%
Undetermined possible causes	7.0%

The time when improvement was first evidenced from our antiallergic therapy averaged 10 days[2,3].

Our realization of pollen allergy alone first occurred in 1940 in a woman of 48 years whose chronic ulcerative colitis has been controlled with pollen desensitization alone for 19 years[2,3]. Moderate bleeding and diarrhea have recurred on three occasions with temporary cessation of this therapy. During this period, six other cases controlled by pollen therapy alone, 18 controlled with such therapy and with elimination diets, and 39 in which pollen allergy was of definite or probable importance have been treated. This increasingly has shown the necessity of studying pollen allergy, especially when symptoms begin in or are exaggerated during the pollen seasons at times fulminating in type during the pollen seasons as we reported in 1955[2]. Though pollen allergy is especially common in California, Nevada and the adjoining states, we are assured that its study and proper treatment in other areas in this and other countries will confirm its role in chronic ulcerative colitis.

Though other inhalant allergy is probable in chronic ulcerative colitis we have not confirmed it in the few cases in which it seemed possible. Evidence of infectant allergy has not arisen.

Activation of chronic ulcerative colitis in a few of our patients has been apparent from certain sulfonamides and vitamins, especially of the B-complex and from Vitamin C. Because of possible drug allergy, discontinuance of formerly used medications has been routine.

In our opinion, psychosomatic symptoms are the result of, rather than the cause of chronic ulcerative colitis. They arise from the uncontrolled distressing and often invaliding chronic ulcerative colitis and complications. As our antiallergic and indicated adjunctive therapy have controlled chronic ulcerative colitis the psychic symptoms have abated. The hypersensitive egocentric, infantile, dependent and resentful personality first reported by Murray[7] in many patients with chronic ulcerative colitis has been infrequent in our experience. As Ingelfinger stated psychic influences are the "easy way out" in explaining chronic ulcerative colitis. The realization that allergy rather than "an unknown cause" explains the disease in addition reassures the patient. Control of schizophrenia in 2 patients occurred with our therapy.

Hypersensitivity of the collagen or autoimmune types is hypothecated by some students. Though this needs study, the patients' welfare today requires adequate and experienced study of atopic allergy as indicated by our good and excellent results in these 20 years.

TABLE II

Grade 4 (most severe)	26.2%
Grade 3	41.0%
Grade 2	30.0%
Grade 1	2.8%

Skepticism of atopic allergy is not justified without an open-minded adequate study of allergy and our antiallergic therapy in more than a few cases for at least a year.

The days of hospitalization in 84 of our 170 cases in whom colonic surgery or death did not occur in the initial period of our supervision varied between 8 and 70 days with an average of 26 days. This was much less than that of some other students or investigators. Thus Kirsner and Palmer[8] in 1954 reported more than 100 hospital days in 48 of 71 cases, over 200 days in 19 cases and 417 to 718 in 4 cases. Their series was studied when the large majority of ours were investigated. In our opinion, our antiallergic therapy was responsible for these shorter periods. The relief obtained in most of the 67 cases of chronic ulcerative colitis treated in our office in our opinion, also supports atopic allergy in the etiology.

The average age of onset was 25.6 years (1-70 years)[3]. There were 14 children up to 15 years of age. The average duration of the chronic ulcerative colitis had been 3.9 years (¾ to 40 years). The degree of chronic ulcerative colitis is indicated in Table II.

It is probable that many in Grade 1 and 2 would have become more severe without the benefit from our antiallergic control.

Good or excellent results in 170 cases were obtained in 49.4 per cent with antiallergic therapy alone and no antibiotics, sulfonamides, ACTH, or corticoids. Patients receiving antiallergic therapy and only sulfonamides 8.2 per cent; only Azulfindine 2.9 per cent; only antibiotics 4.7 per cent; sulfonamides and antibiotics 8.2 per cent; sulfonamides, ACTH and/or corticoids, 9.4 per cent. Thus 81.6 per cent or 139 of our 170 cases received good or excellent results with antiallergic therapy with or without the above drugs and hormones. This number was reduced by the inclusion of patients who died before antibiotics were available. It is also probable that present improved antiallergic and adjunctive therapy would have relieved some of the 8 patients whose degree and time of cooperation were inadequate. In 22 patients treated since the tabulation of our results up to 1958, no failures in our therapy, no deaths, and no colon surgery have occurred, except in one patient who had advanced cirrhosis and who died 2 weeks after colectomy in another hospital.

TABLE III

RECURRENCES AND EXACERBATIONS IN 170 CASES UP TO 1958

Explained by breaks in the diet in	47 patients
Explained by depression, refusal to eat and infection (in 1945) in	1 patient
Explained by inadequate therapy in	23 patients

The greatly reduced recurrences in our series compared with those of other investigators have been due in our opinion, to the supervision, treatment and policing of all of our patients from the allergic viewpoint. Cooperation in our therapy varied from less than ¼ year (11 patients) to 19 years with an average of 3.3 years (total 556 years).

The arthritis, chondritis of the ear, *erythema nodosum*, iritis, hemorrhage from the colon in 2 cases, parotitis, *pyoderma gangrenosum*, schizophrenia, and thrombophlebitis in 6 cases were controlled during our antiallergic and adjunctive therapy. Since the sulfonamides and antibiotics and especially the hormones were given in relatively small doses, the latter only in 9.4 per cent of our cases, the control of these complications in our opinion was largely or entirely due to the antiallergic therapy. Thus severe, invaliding arthritis, and fever in one man disappeared with the control of his chronic ulcerative colitis in one month with our elimination diet and formerly ineffectual sulfonamides and salicylates. For the last 15 years the arthritis and chronic ulcerative colitis have been controlled with the diet alone. A woman with severe ileocolitis and a previous ileocolectomy, invalided for nine years, especially with long-standing, crippling arthritis in knees, ankles and feet was relieved in one year and has remained entirely

symptom-free for the last seven years with pollen desensitization alone. *Erythema nodosum* in the legs of one woman disappeared in one month with the proper elimination diet alone. It also disappeared in another woman in one month with control of food and pollen allergy. Our two cases of severe *pyoderma gangrenosum*, especially in a man of 38 years[2e], came under gradual control with our elimination diet and with no antibacterial or hormone therapy.

Pregnancies in 8 women, two in each of 4 patients, were normal with no activation of the colitis or complications. With our antiallergic therapy the chronic ulcerative colitis was controlled. One erythroblastic infant died.

The relative infrequency of cancer (1.2 per cent) in our series similar to the reports of Bargen, Kirsner, Brown et al, contraindicates routine total colectomy to prevent its origin. Greater frequency arises in clinics where prediagnosed carcinoma or patients with long-standing invaliding chronic ulcerative colitis are

TABLE IV

COMPLICATIONS[3]
(OTHER THAN FEVER IN 45 PATIENTS)

Arthritis	4.0%	Necrotic reaction to vaccine	2.0%
Cancer of colon	1.2%	Parotitis	0.6%
Chondritis of ear	0.6%	Perforation of colon	4.0%
Erythema nodosum	4.0%	*Pyoderma gangrenosum*	1.0%
Fever	56.0%	Rectovaginal fistula	8.0%
Fistula (anorectal)	5.0%	Schizophrenia	1.2%
Hemorrhage from colon	3.0%	Thrombophlebitis	8.0%
Iritis	0.6%	Pregnancy (2 in each of 4 patients) of women	18.0%
Stricture	3.5%		

referred. It did not arise in 42 of our patients with chronic ulcerative colitis of 8-40 years' duration or an average of 17 years. They cooperated in our therapy for an average of 11 years. Of these 9 had chronic ulcerative colitis for 20-30 years or an average of 24 years and 3 had it for 30, 31 and 40 years respectively. Thus colectomy to prevent cancer when chronic ulcerative colitis has lasted more than 10 years is not justified especially if cooperation in our therapy continues.

In our opinion, the study and control of allergy in all our cases of chronic ulcerative colitis has reduced or controlled chronic irritation of tissues with the resultant reduction in cancer.

Most of the 11 ileostomies with or without colectomies before 1957, in our opinion, could have been prevented today with more adequate and understanding cooperation in our antiallergic therapy, helped in some cases by our present antibiotics and corticosteroids. In the same manner we are of the opinion that most of the surgery since 1947 could be obviated today except: 1. for the formerly reported perforation of the sigmoid[2e] after the well controlled patient's

insistence on cortisone to enable her to eat foods off her beneficial elimination diet; 2. for the cancer in the glands of the hepatic flexure in one case and 3. for the ileosigmoidostomy with subtotal colectomy to control colonic bleeding lasting four weeks[3]. For 6 years before and for 4 years since this surgery, her chronic ulcerative colitis was and is still controlled with our antiallergic therapy.

It is probable in our opinion that larger and more prolonged doses of corticosteroids and continued or revised pollen therapy might have made three of the partial colectomies unnecessary. In the last 2 years since compilation of these statistics, no surgery has been necessary in these reported cases or in additional cases cooperating in our therapy except to relieve ileal obstruction in one

TABLE V

ILEOSTOMY AND/OR COLECTOMY[3]

I. Ileostomy done before 1947:	
(1) Advised antiallergic therapy not given	2
(2) After stopping beneficial antiallergic therapy	1
II. Ileostomy and colectomy before 1947:	
(1) Unsatisfactory results from antiallergic therapy	3
(2) After stopping beneficial antiallergic therapy	5
III. Ileostomy and colectomy after 1947:	
(a) Failure of antiallergic therapy	3
(b) Perforation of sigmoid after cortisone therapy	1
(c) Cancer of glands in hepatic flexure	1
(d) Severe hemorrhage and hemolytic staphylococcic infection of colon	1
(e) After stopping of beneficial antiallergic therapy	4
IV. Colectomy distal to mid-transverse colon and final colectomy in one case due to failure to control probable pollen allergy	5
V. Ileosigmoidostomy with subtotal colectomy because of hemorrhage. (Chronic ulcerative colitis controlled with antiallergic treatment)	1

Ileostomies and colectomies previously advised and prevented with our antiallergic therapy—19

patient with a former total colectomy. In the last 2 years surgery and death have occurred in other hospitals in 2 men whose cooperation in our antiallergic therapy had been very inadequate.

In these operated cases control of former or probable atopic allergy has been continued or advised to prevent postoperative complications or extension or development of regional enteritis.

Surgery has not been done in fulminating chronic ulcerative colitis since 1947 except in one patient with severe hemorrhage and a hemolytic staphylococcic infection of the colon[3], and in only two such cases before 1947. At present

more transfusions and antibiotics would be given for more than one week before such surgery, hoping that these with antiallergic therapy would prevent such emergency colectomy. We also suggest persistent atopic allergy as a possible cause of complications in the ostia or small bowel after colectomy.

There were 10 deaths before 1947: three after ileostomies before our present knowledge about the control of electrolytes, five from peritonitis before present antibiotics were available and two after the discontinuance of our beneficial antiallergic therapy.

From 1947 to 1958 the five deaths have not resulted from chronic ulcerative colitis. One occurred from cancer of the colon, one from perforation of a duodenal ulcer after cortisone therapy in a man of 78 years, one from hepatic coma,

TABLE VI

DEATHS[3]

I. After ileostomies (before 1947)	3
From peritonitis in first two weeks of treatment (before 1947)	4
From perforation and peritonitis after ileostomy following 3 months of antiallergic therapy (before 1947)	1
II. Following ileostomies and colectomies after stopping our successful antiallergic and adjunctive therapy: (before 1947)	2
From metastases and peritonitis due to cancer of colon in chronic ulcerative colitis well controlled with elimination diet	1
From perforation of duodenal ulcer during cortisone therapy in man of 78 years	1
III. In patients well controlled with elimination diets:	
(a) From hepatic coma due to hepatitis	1
(b) From metastasis from cancer of pancreas	1
(c) From peritonitis from Christian Science treatment (previously controlled with our diet)	1

one from cancer of the pancreas, and one during Christian Science treatment in a man previously well controlled with our elimination diet. In the last two years moreover no deaths have occurred in cooperating patients in these 170 cases or in the additional 22 cases treated since 1957.

Study and Control of Food Allergy

Food allergy should be studied in all cases of chronic ulcerative colitis in which symptoms are not confined to the pollen season. The history of possible food dislikes or disagreements in 56 per cent of our 170 cases also justified such study. This is significant in about 30-50 per cent. Allergy to milk is especially common, as suggested in 35.3 per cent of our patients. Skin reactions were usually negative to allergenic foods[11]. Positive reactions moreover infrequently indicated clinical allergy.

1. If milk allergy seems possible, it alone may be excluded. This has to be complete excluding every trace as in butter, margarine, bread, or other foods. Persistence of foods in the body even for several weeks must be remembered.

The necessary accuracy in the diet in this serious disease is illustrated by the activation of chronic ulcerative colitis even from traces of milk in bakery products, butter, oleomargarine, and especially from small or even occasional spoonfuls of ice cream, sherbet, or other foods containing milk. We confirm Andresen's report of rapid diarrhea from a few drops of ingested milk. We have found similar extreme allergy to other foods, including egg, beef, wheat, coffee, and especially fruits and condiments.

Inhalation of foods by their air-borne molecules also activates chronic ulcerative colitis in exquisitely sensitive patients. Thus severe bleeding, colitis and fever recurred from the odor of tomatos during their canning, requiring 6 transfusions. Lesser bleeding from the odor of apples in an orchard for five hours occurred in this same patient. Chronic ulcerative colitis in one patient was seriously activated after the inhalation of odors of paint and again of lacquer. Here long-standing, invaliding chronic ulcerative colitis had been controlled by her indicated elimination diet and pollen therapy.

2. If milk allergy alone is unlikely or if no evidence of relief occurs in two weeks with its exclusion then the writer's fruit and cereal-free elimination diet[9] plus rice, at times minus legumes is ordered. If this fails or if the chronic ulcerative colitis is severe or fulminating our minimal elimination diet containing lamb, chicken, rice, white potato, tapioca, salt, sugar, water, synthetic vitamins, and calcium carbonate is immediately utilized. With extra strained meat and sugar, 2,500 calories and up to 100 grams of protein a day can be given. With nausea or anorexia, our strained meat formula[10,17] with extra sugar can be intubated for several days.

The preparation of menus, recipes, the necessary cooperation, adequate use, maintenance of weight and nutrition and the adding of foods after relief is obtained has been discussed in former publications[2,3,9,11]. The strict and continued adherence to the diet is most necessary. The physician must supervise and police the patient to prevent slight deviations.

Pollen Allergy

Pollen allergy alone is indicated by the onset and recurrence of chronic ulcerative colitis during the pollen seasons[2,5]. It may also be associated with perennial symptoms due to food allergy. Two cases started following intradermal tests with pollens. In one severe case of chronic ulcerative colitis, hemorrhaging of 3,000 c.c. in 24 hours started in six hours after 40 large positive scratch reactions with pollens. Since then, fewer initial scratch tests are done if pollen allergy is suspected. Skin reactions may be slight to large or absent. They were positive in 13 of our 170 patients whose chronic ulcerative colitis was not due

to pollen. If the history indicates pollen allergy even with negative reactions, desensitization is important. Its presence must gradually be proved by resultant relief. The multiple antigens, the indicated doses, the time of administration and the length of such therapy are discussed elsewhere[25]. Pollen filters in the home or moving to areas with little or no pollen as on the seashore are helpful.

Since our first case due to pollens was recorded in 1942, our increasing recognition of pollen allergy has been noted in all of our other publications. Good or excellent results from this therapy have been reported and continue up to the present time. As recently reported, however, there have been four cases in which partial and in one case final total colectomy have been done because of increasing symptoms in spite of desensitization to apparent pollen allergy. This failure also occurs with desensitization to other inhalants, causing other allergic manifestations, especially atopic dermatitis. With increasing knowledge and ability in this therapy and with larger and more continued doses of corticoids such surgery should be reduced. It is also possible that inhalants other than pollens were unrecognized in these operated cases.

Adjunctive Therapy

Antibiotics have been important but only when secondary infection has needed consideration. The effect of sulfonamides including Azulfidine has been questionable and never curative in our cases. The control of fever in 36 per cent of 96 of our patints with antiallergic therapy alone without antibacterial or hormone treatment indicates that allergy also was probably responsible for fever in other patients who were given small doses of these drugs.

In these 170 patients corticoids and/or ACTH were given to only 22 patients during the first weeks in severe cases or during exacerbations, and in small doses at times during the pollen seasons. Benefit was evident in only 14. No hormones were used for our good results before 1950. Since then benefit has been moderate or questionable in only 14 of 22 patients receiving them. Large doses of 20 to 40 mg. of prednisone or its equivalent in other corticoids however were not used. During the last two years corticoids have been given by rectum and mouth in two fulminating cases (Case 4), discontinuing it in 2 to 4 weeks respectively as antiallergic therapy became effective. Oral may prove as effective as rectal therapy and as beneficial as intramuscular administration except when vomiting or extreme fulmination of symptoms exist. We stress the importance of antiallergic therapy in all patients receiving these hormones in order to control the chronic ulcerative colitis without their use. Their recognized complications including duodenal or other gastrointestinal ulcerations or perforations and psychoses must be remembered.

Anemia, bleeding and hemorrhage require recognized therapeutic measures. Colectomy for hemorrhage should be combated with transfusions for one or even two weeks, Vitamin K, and corticoid and especially antiallergic therapy.

Ileostomy and colectomy have already been discussed. In two of the few patients with ileostomies alone whose continued ileal discharge and cramping with rectal blood and mucus were controlled by our antiallergic therapy, rejoining of the ileum with the colon has resulted in normal colonic function for 8 and 16 years respectively. This suggests that ileostomy alone may still be advisable, anticipating such reunion of the ileum and colon after control of the chronic ulcerative colitis with antiallergic and if necessary hormone and other adjunctive treatment. We are assured, moreover, that adequate and experienced antiallergic therapy will definitely reduce ileostomies with or without colectomies. No case of chronic ulcerative colitis should be denied its very probable benefit or control especially before ileostomy or irreversible colectomy is done.

Case Histories

The first case illustrates the control of chronic ulcerative colitis with the elimination diet alone with no antibiotics, sulfonamide, ACTH, or corticoid therapy. The necessity of antibiotics in Case 2 and of sulfonamides in Case 3 is questionable.

The fourth case was also given such adjunctive therapy including a corticoid by rectum hoping to hasten recovery. Thus discontinuance in one week after leaving the hospital and the perfect control of her chronic ulcerative colitis with antiallergic therapy alone for 9 months even with her present 3 months pregnancy supports allergy alone as the cause, as is evidenced in the first 3 cases and those reported in our previous articles.

Case 1:—Chronic ulcerative colitis due to food allergy—Chronic ulcerative colitis for three and one-half months. Loss of 40 pounds. Sulfonamides caused dermatitis. Penicillin increased diarrhea. Life-long dislike for milk. Food allergy indicated by relief of diarrhea with the elimination diet with no drugs or antibiotics and continued control for nine and one-half years with elimination of milk, egg, and fruit. Increase of weight in hospital up to 185 pounds in 1954 and has held at this weight since that time. During these last 11 years her chronic ulcerative colitis has been perfectly controlled except for one brief recurrence from break in diet.

Case 2:—Chronic ulcerative colitis for 2 years. Pollen and probable food allergy—A woman of 33 years was first seen in July, 1955 in the Merritt Hospital because of chronic ulcerative colitis starting in June, 1954. Symptoms had subsided until cramping, slight fever and blood again recurred in May, 1955. These continued along with *erythema nodosum* on the legs and pains in many joints.

Former gastrointestinal and allergic symptoms were absent. Hay fever was present in her sister. Diet history revealed a long-standing dislike for milk. All examinations were negative except for a low serum prothrombin, hemoglobin and RBC. One-plus reactions were obtained to several spring and fall pollens. Proctoscopy and x-ray of the colon confirmed chronic ulcerative colitis.

Probable pollen allergy was studied with desensitization to a multiple pollen antigen and with a pollen filter in the hospital window. Food allergy, especially to milk was studied with our fruit and cereal-free elimination diet plus rice. Antibiotics were given in the first ten days along with two transfusions. All symptoms, including the *erythema nodosum*, were controlled in one month and have been during the last four years with pollen therapy and with the elimination of milk, uncooked vegetables and fruits from her diet. In our opinion, both pollen and food allergy are responsible for her chronic ulcerative colitis.

Case 3:—Fulminating chronic ulcerative colitis due to food allergy controlled for 18 years—A man of 38 years first developed chronic ulcerative colitis in May, 1939. It was fulminating in 2 months with *pyoderma gangrenosum* on the abdomen, an ischiorectal abscess and fatal prognosis. After gradual improvement, 3 to 5 liquid at times blood stools continued. Another fulminating attack with *pyoderma gangrenosum* on the neck and feet occurred in April, 1941. A post-mortem permit was signed. In consultation I ordered my fruit-free elimination diet in spite of his desperate condition. Decrease in stools and fever and recovery occurred in 1½ months. Our experience indicates that the fever may have disappeared without the sulfaquamidine.

In the last 18 years, his chronic ulcerative colitis has been absent except for fulminating attacks in 1942, 1945, and 1950 when forbidden milk, fruits and condiments were eaten. With his strict elimination diet and pollen therapy, he has been perfectly well, has worked in a factory daily, at times 7 days a week and 10 hours a day during the war.

Comment:—The rapid relief in 1 month from a fatal prognosis with perfect control since 1942 except for 3 recurrences after breaks in diet emphasizes the food allergy and the study of atopic allergy in all cases of chronic ulcerative colitis. The onset in the spring of 1939 and its recurrence in the spring of 1941 also justified pollen therapy though food allergy has proved of major importance.

Case 4:—Severe chronic ulcerative colitis due to food and probable pollen allergy—A woman of 27 years suddenly in June, 1958 developed 4 to 5 loose, bloody stools, anorexia, nausea, increased cramping and pain in the lower abdomen and anus and an increase of such stools up to 20 a day. A one-month premature baby was born. A bland diet with sulfasuccidine up to 10 grams daily and corticosteroids for a fortnight were ineffectual. Chronic ulcerative colitis was diagnosed by x-ray and proctoscopy. Colectomy and psychotherapy were advised.

Her family and personal histories were negative for allergy except infantile eczema. She had always disliked milk.

Physical examination was negative except for diffuse abdominal and anal soreness. Laboratory tests were negative except for 2 plus reactions to grass pollens and house dust with no reactions to foods.

Treatment:—To study food allergy our minimal elimination diet and vitamins were ordered. Because of fulminating colitis, corticoids by mouth and rectum were given. The effect of Chloromycetin and Azulfidine was questionable.

With improvement in 10 days, ginger ale was given by mistake. In 2-3 days fulmination recurred. With its elimination and continued antiallergic and adjunctive therapy, relief again occurred in 10 days.

In the last 8 months, constipation occurred in the first 2 weeks. Since then no medications have been given. She has had 1-2 formed daily stools, has gained 10 pounds, does her own house work, cares for her 2 babies, is two months' pregnant and is entirely comfortable. Proctoscopy 4 months ago showed slight mucosal edema with no blood or ulcerations. X-ray of the colon showed a nonhaustrated descending colon devoid of feathery appearance and evidence of polyposis compared with the marked diffuse acute chronic ulcerative colitis before treatment*.

She is on her elimination diet plus rice, beef, oats, turkey, carrots, squash, peas, peaches, pear and egg. She is receiving hypodermically a weak multiple pollen antigen at present in the 1:500,000 dilution each week.

Comment:—The failure of previous sulfasuccidine and corticoids and the perfect control of her chronic ulcerative colitis with the elimination diet and the multiple pollen antigen suggests that this result would have arisen with the antiallergic therapy alone as it has in 49.4 per cent of our 170 cases.

Summary

1. Our study and treatment of chronic ulcerative colitis for 20 years indicates vasculitis and resultant thromboses and necroses from allergic inflammation especially to foods, less often to pollens and occasionally to drugs as the major cause. Allergy to other inhalants needs study. Infectant allergy is not evident.

2. The colon may be the only shock organ of allergy. The family, personal or diet history may reveal no allergy.

3. Secondary infection, anemia and avitamosis may be complications.

4. Of 170 cases of chronic ulcerative colitis 49.4 per cent were controlled with antiallergic therapy alone with no sulfonamides, antibiotics, ACTH or corticosteroids.

5. These hormones should be used only with adequate antiallergic therapy to control the chronic ulcerative colitis without their use.

6. In the last 11 years no deaths have occurred in cooperating patients from chronic ulcerative colitis alone. Ten colectomies were due to our present inability

*In June, 1960 her colitis is perfectly controlled. A third pregnancy occurred with no colitis. She is still on her elimination diet. Pollen therapy has been stopped.

to control all probable allergy, especially to pollens and in part to irreversible pathology.

7. Since 1957 there has been no surgery and no deaths in 22 additional cases of chronic ulcerative colitis cooperating in our treatment except for ileal obstruction in a man with a former colectomy.

8. Our results emphasize the importance of adequate and experienced study and treatment of allergy in all cases of chronic ulcerative colitis, especially before irreversible colectomy.

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Discussion

Dr. Julius Bauer:—Well, gentlemen, the first most interesting report of Dr. Ives reminded me of a similar symposium which was held 25 years ago in Vienna. The participants were internists who spoke about the psychosomatic, the psychological, the neurogenic aspects of peptic ulcer, and when the discussion was over the chairman, a very witty gentleman, said, "Well, if I may summarize the point of view of the surgeons, we are going to continue to operate on the stomach and not on the brain."

We know that neurological disease may cause manifestations in the gastrointestinal tract. Of course in every organ it can do that.

So far as Dr. Mohr is concerned, I must congratulate him particularly on his concept of consideration of many etiological factors. He gave us a good modern concept of the psychological factors involved in ulcerative colitis. But Dr. Mohr knows very well that not everybody who needs a psychiatrist will blindly accept the psychoanalytical concept, and what has been found in analyzing people with ulcerative colitis, particularly the work of Alexander, indicates that many times it is personality factors, frustrations, insecurity, hostilities. But where are the controls? Who analyzes the same way what we call normal people? Who among us can determine who is normal? I consider us perfectly normal people, but who among us has not had any personal difficulties of some kind, frustrations, hostilities against the boss, a family member or what not, or even felt insecure at some time?

Well, I don't think that those factors can be considered as specific features of ulcerative colitis.

Autonomic nervous imbalance is where the excellent exposition of Dr. Rowe comes in, the allergic factor. I am quite sure this allergic factor is a most important one, and I think he is to be congratulated on the most excellent results of his treatment. In my opinion, ulcerative colitis is a manifestation of a more general type of allergy.

Food allergy is certainly to be considered in all cases of ulcerative colitis, but if we hear of food allergy as a rule we don't expect ulcerative colitis. Food allergy presents quite a different picture, so it requires also some particular explanation. Why does food allergy manifest itself as ulcerative colitis?

Of course today, in our present age, we try to overestimate all things which we can't interpret, which we can't explain. Well, whether the explanation is correct or not, that is a secondary question, but those are the questions I would like to ask Dr. Rowe, whether actually it is proved that it is a specific allergy which he has found, or whether it is merely hypersensitivity of some type? And then, what causes a particular predisposition, thus occasioning food allergy to respond with ulcerative colitis?

Question:—I would like to ask Dr. Mohr if he has had an opportunity to study any of these children who had colectomy performed and then studied them psychologically.

Dr. Clarence J. Berne:—The question is directed to Dr. Mohr. Would you like to comment on it first, Dr. Bauer?

Dr. Bauer:—I think it is better for Dr. Mohr to respond.

Dr. George J. Mohr:—I have had no opportunity to study such children. I would venture a guess that if they are children who have had ulcerative colitis—such a child should be capable of garnering his psychological resources just as he is capable of garnering his other physiological resources in the service of further development, but I have no such evidence.

Dr. Berne:—I think the answer is perhaps indicative of the fact that if one goes to the literature of psychiatric studies on people who have been rehabilitated by colectomy and who have good results we will find studies on those people before and after are very, very varied.

Are there any other questions?

We have a written question addressed to Dr. Mohr: "Dr. Mohr, do these same mechanisms as described by you in children apply to adults who develop ulcerative colitis?"

Dr. Mohr:—The early life history, the early experience of adults with ulcerative colitis, is very similar to that which we find in children, at least as well as one can reconstruct these in dealing with adults. One gets a clearer picture with children because they are closer in point of time to the disappointing experiences, and so often one can actually study and get to know the mother of the child. I would say the basic reactions of the adults to care, the nature of the early disappointments and frustrations they have experienced, show a great similarity to what is observed among children.

Dr. Berne:—We have two questions addressed to Dr. Rowe. First, "Why are people allergic?"

Dr. Albert H. Rowe:—Though a manifestation of allergy may arise with no apparent history of clinical allergy in the previous one or two generations, such a family history is usual. If such inheritance is on both sides, the manifestation may be more definite and occur earlier in life as in childhood than if it is unilateral. The inheritance may predetermine a specific manifestation such as asthma or hay fever or a type of allergy as to foods, even to specific foods or to pollens. Thus there is often a familial tendency to gastrointestinal allergy. We have histories morever of chronic ulcerative colitis and regional enteritis occurring in siblings or in two generations.

Dr. Berne:—We have another question. "If allergy is a major factor in chronic ulcerative colitis why are corticosteroids no more effective than reported?"

Dr. Rowe:—It is known that corticosteroids and ACTH reduce or block inflammatory reactions in tissues arising from infections and especially from the many causes of allergy. This effect continues to be reported in chronic ulcerative colitis and also in regional enteritis, not only from oral and parenteral but also from rectal administration.

This beneficial effect, in part, favors allergy as a major role in chronic ulcerative colitis and regional enteritis, especially because infection has not been the accepted cause.

Our study of allergy and results with antiallergic therapy increasingly during these 20 years support an allergic eczematous-like inflammation of all layers of the colon from atopic allergy as the major cause of chronic ulcerative colitis. The erythema, granularity, oozing of serum, friability of membranes and even bleeding seen in chronic ulcerative colitis through the proctoscope also occur in severe, acute, atopic eczema. Students of chronic ulcerative colitis should confirm this similarity by seeing for themselves such cases of acute allergic eczema or dermatitis.

The continued vascular allergy moreover best explains the varying ulcerations, necroses, scar tissue formation, and occasional perforations with or without secondary infection.

If chronic ulcerative colitis is due to an eczematous-like inflammation, the same causes of allergic eczema, especially food and pollen allergies should be responsible for chronic ulcerative colitis. Our reports in the literature have long confirmed these causes.

The role of food and pollen allergy was demonstrated especially in a girl of 13 years, when first seen by Dr. Uyeyama and by me in the University of California Medical Clinic, and reported above in this article. Because of chronic ulcerative colitis for many years, an ileostomy had been done for over a year. Liquid, ileal discharge, and bloody rectal expulsions continued. Odor from the poorly fitting bags had ostracized her from friends, school and church with resultant depression and threat of suicide. With the proper elimination diet and pollen therapy, with no corticoids and no antibiotics, the ileal and rectal discharge decreased in one month. Rejoining the ileum and proximal colon in 9 months resulted in normal colonic function in another month. For 10 years her chronic ulcerative colitis has been perfectly controlled even during and since pregnancy three years ago. Her very sufficient elimination diet and pollen therapy have continued. If this control of allergy had occurred before ileostomy was contemplated, it would not have been necessary to perform surgery. Her normal personality and freedom from depression since the normal bowel channel was

re-established shows that the psychological disturbances were secondary to the chronic ulcerative colitis uncontrolled by surgery.

Adequate experienced study and control of atopic allergy therefore should precede all surgery even in fulminating or long-standing chronic ulcerative colitis.

Dr. Berne:—We haven't had a good argument today, and this maybe will stir up one. This is addressed to Dr. Mohr: It asks, "Dr. Mohr, what is your interpretation of the psychological interpretations of Dr. Rowe's treatement?"

Dr. Mohr:—I think Dr. Rowe has made a significant psychological contribution to our understanding of ulcerative colitis. I have been most impressed.

I plead ignorance with respect to the allergic component in ulcerative colitis as such.

I must confess, Dr. Rowe, we are studying a group of allergic children who are suffering with eczema and asthma, not ulcerative colitis. We are working very closely with allergists. We are attempting to document as precisely as we can—not we ourselves, but experienced allergists—just what the story is with respect to the allergic component.

Our perspective is that one is confronted with highly complicated problems dealing with allergic conditions, eczema and asthma, in children, or ulcerative colitis, if the latter is to be included among allergic disorders. I simply accept what Dr. Rowe says as having the authority of his many years of experience as an allergist.

But if you ask me about a psychological or psychiatric response to Dr. Rowe's report, I would say that one—one—of the elements that probably plays a significant role in his therapeutic program is that Dr. Rowe brings into his relationship with these patients something that they need urgently—authority, conviction, and assurance that their needs are being met. While all sick people need such assurance, it has most specific meaning for the ulcerative colitis patient whose illness is concomitant with feelings of helplessness and hopelessness. People might want to argue about the allergic aspect, as to whether this is a specific allergic reaction or whether one is dealing with some general constitutional consideration. But I was listening to Dr. Rowe as a psychologist—not I as a psychologist but he as a psychologist. He meets basic needs and in so doing stress is diminished for the patient. I assume that if one avoids certain irritating allergic substances one relieves the individual of certain stress. This is patent enough in how one protects patients against pollens or foods to which they are sensitized either by elimination or by desensitization. Dr. Rowe's methods cut down a great deal on one element of stress as it involves reactions at a certain level; that is, reactions in terms of the mucosa of the gastrointestinal tract.

I would say anything that cuts down on the over all stress that the individual is subjected to may be helpful.

Dr. Rowe speaks from an etiological standpoint. He says, "This is the cause of the illness and we remove the cause of the illness." He may be right. Speaking, however, from the psychological standpoint, we simply have to emphasize the fact that there are a multiplicity of factors that enter in, all of which contribute to the state of stress. These may include the constitutionally determined predisposition to allergic reactivity.

Non-allergists are more likely to point out the fact that allergic reactions, especially in children, are fluctuating. I would like to suggest to Dr. Rowe that some combined studies of these cases by allergists and psychiatrists, not for the purpose of proving who is "right" or "wrong," but from the standpoint of ascertaining the order of conditions or events that would seem to be significantly related to predisposition to the illness, the nature of precipitating events and, if possible, circumstances that determine recovery. We are quite convinced that characteristic life circumstances are concomitants of the illness, as may be allergic or other forms of physiological reactivity.

What shall we say about the ulcerative colitis patient who has been advised to have an operation, but undertakes psychotherapy and in the course of a year clears up, and goes on to have a baby exactly as did the patient reported by Dr. Rowe? No attention had been paid to the diet. Does that disprove anything in relation to Dr. Rowe's work? Not at all.

I would say we must look into such cases. Can it be that the other case was not an allergic case? Or maybe one might demonstrate that the same allergies exist but that the reduction of stress through psychotherapy permitted the re-establishment of an equilibrium with alleviation of the symptoms of ulcerative colitis.

Dr. Berne:—I am under orders to stop at a certain time, but I do have some more questions.

Before going further, as Moderator I would like to take a moment to point out that from the discussion about psychological versus allergic and other factors it is clear that all may, in theory, be responsible.

Now it is not, I think, incorrect to consider that while the answer to the etiology of this disease is far away from us today, it isn't a matter of whether allergy alone or psychological factors alone can be proven to be responsible. A good many other things may enter, and in this category we always have to remember that we do not know the ultimate cause of anything, so I think it is well that we put some of these things together.

Now there are three questions left addressed to Dr. Rowe, and I think I will have to ask these gentlemen to ask them of Dr. Rowe privately, and we will declare an intermission.

CHRONIC ULCERATIVE COLITIS AS VIEWED BY THE INTERNIST*

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Introduction

Chronic ulcerative colitis is a nonspecific systemic disease with a local lesion. It begins usually in the rectosigmoid and progresses relentlessly craniad. It is not familial, has equal sex distribution and may occur at any age, though usually in young adults. Only irritable colon is a more frequent cause of chronic diarrhea[1]. Of 99 patients hospitalized with chronic diarrhea, 41 were found to have ulcerative colitis[2]. The first sign of rectosigmoid colitis, however, is frequent bloody fluxes with constipation[3]. The latter is due to protective rectal spasm and resultant tenesmus. As the entire large bowel becomes involved, there is a change from mixing-absorption motility to a propulsive-excretory type, and true diarrhea (two or more fluid fecal movements daily) results[4].

Etiology

Etiology of chronic nonspecific ulcerative colitis is unknown. It may be a collagen disease with psychosomatic features, as rheumatoid arthritis or *lupus erythematosus*[3,5,6]. Similar mucosal lesions occur with bacillary dysentery, amebiasis, lymphopathia and avitaminosis. The common pattern suggests that all response is characteristically to a noxious agent of molecular, rather than bolus, size. Although an infectious agent has not been proved, an altered tissue reaction to an organism, as in rheumatic fever, has not been excluded[3,7]. A hyperimmune mechanism may explain the thromboses[8], lymphatic dilations, perivascular infiltrates, granulomas, giant cells, tissue eosinophilia and hemolytic anemia[9]. Other histologic features of possible etiologic significance include vasculitis and cryptitis[10], endothelial desquamation[11], changes in basement membrane[5], degeneration of epithelial cells[12] and hyperfunction of mast cells[13]. Such findings are usually limited to less than 50 per cent of the series studied, and are not readily reproduced by independent investigators.

Direct observations of right colon activity with left colon disease revealed petechiae and tranquility[3,14]. Vascular changes were not a result of muscle spasm. Situations of abject fear and dejection were associated with hypofunction of large intestine, with pallor, relaxation and lack of contractile activity, whereas situations of conflict, with anger and hostility, disclosed hyperfunction of intense frequent waves, with thick tenacious mucus, petechiae and fragility of mucosa.

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Studies of the myenteric plexus of colitis patients have revealed a twofold increase over normal number of ganglion cells[15]. Whether this is a congenital or acquired defect is unknown. Destruction of ganglion cells with colonic dilation may result from overwhelming toxicity[16].

Pathophysiology

Grossly, the rectosigmoid is the most frequent initial site, followed by the descending, transverse and ascending segments of the colon. Spreading is not dependent upon continuity with small bowel, and identical changes may occur in the ileum after colectomy.

Initial miliary abscesses and petechiae are followed by bleeding, granulation, ulceration and pseudopolyps. Exudative hypersecretion, hypermotility, malabsorption and possible toxic absorption result from the mucosal-submucosal dysfunction[3]. Essential nutrients, electrolytes and fluids are lost. Radiosotope studies suggest a malabsorption of protein and fat during an exacerbation[17]. Negative nitrogen balance and avitaminosis lead to hepatic, renal and pancreatic insufficiencies. Loss of sodium, potassium, chloride and calcium may result in either metabolic alkalosis or acidosis. Water loss can exceed 5,000 c.c. daily. Metabolic exhaustion is evidenced by lowered urinary 17-ketosteroids[18].

Symptoms

Ten to 20 rectal discharges of blood, pus and mucus, with cramps, tenesmus and weight loss, comprise the cardinal syndrome.

Three clinical forms exist[18]. Sixty-eight per cent are chronic intermittent, with active annual episodes of 4 to 12 weeks. This type may evanesce after five years. Twenty-six per cent are chronic continuous, which leads to increasing periods of prolonged disability. Acute fulminating colitis occurs initially in 6 per cent of patients or during any active period of the other two types. It is extremely toxic and febrile, with colon necrosis and visceral peritoneal involvement. Patients are moribund. Paradoxically, persistent rectal discharges then occur in the presence of a toxic megacolon[16,19].

Severe headache is a common accompanying symptom not often recognized in the literature[20].

Diagnosis

Diagnosis is partly dependent upon the patient's history, emotional background, mode of onset and state of nutrition.

Rectal digital examination may reveal a tight outlet with a "cobble-stone" or granular mucosa.

Proctoscopic examination is diagnostic in 95 per cent. Involvement in the remaining 5 per cent is beyond view of the instrument[18,21]. The earliest change

is hyperemia, followed by a mottled discoloration due to petechiae. Many bleeding points with oozing occur and ulceration results, with or without granular mucosal bridges and pseudopolyps.

Radiologic abnormalities may not be apparent in over 30 per cent of first barium enemas[22]. Initially the mucosa is fuzzy, feathery or finely serrated. Later haustral markings and mucosal pattern are lost, and finally narrowing and shortening appear, with loss of flexures. The entire colon is involved in 50 per cent of patients[18]. Small bowel studies are always necessary to determine the extent of disease, as the ileum may be involved in 34 per cent.

Complications

Complications are divided into colonic and extracolonic[23]. The frequency of the former are: pseudopolyposis 19, stricture 11, malignancy 6, perirectal abscesses and fistulas 6, perforation 2 and hemorrhage 1 per cent.

Extracolonic complications involve multiple systems and include thrombophlebitis, nephritis, hepatitis, pancreatitis, arthritis, iritis, scleritis, *pyoderma gangrenosum, erythema nodosum,* nutritional edema and anemia.

Treatment

Most patients respond well to properly administered rest, antidiarrheals, blood, fluids, vitamins, diet and anaclitic therapy.

Bed rest is essential because physical activity increases intestinal peristalsis. Hospitalization also removes patient from noxious influences of environment which more than likely contributed to his attack[21].

Loose stools and cramps may be controlled with mild opiates, as codeine or tincture of opium. Patient should be encouraged to voluntarily retain colon content by contracting his external sphincter and levator ani musculature.

Whole blood is necessary, not only to correct microcytic or hemolytic anemia, but to halt and reverse the negative nitrogen balance. Though reactions to blood are common, 20 or more transfusions may be necessary during a severe relapse[15]. Oral iron is not well tolerated, but intramuscular preparations alleviate true iron deficiency.

Intravenous fluids should halt and reverse abnormalities of sodium, potassium, chloride, calcium and urea. Six liters daily may be necessary until urine output exceeds 1,500 c.c. Vitamins should be included in intravenous, as well as oral, regimes.

Diet should rapidly exceed 3,000 calories, with 150 gm. protein. Frequent visits of dietitian to patient are necessary and help to avoid such mistakes as a tray of pureed slush[21].

Anaclitic therapy, referred to as TLC, is of much value[3,15,21,24,25]. Establishing a good doctor-patient relationship through kindness, encouragement and firm reassurance instills confidence and attachment to a "father-figure". Physician should not betray anxiety and should announce all program changes. Patient needs to ventilate and discharge aggressive feelings. Physician wisely excludes all personnel and visitors who annoy, and as patient improves he cuts the bonds of anacliticism.

Antibiotics and chemotherapy are nonspecific, though presumably helpful, during toxic febrile periods and for complications, as perforations, abscesses and pericolitis. Azulfidine is reported to have a beneficial effect on connective tissue dysfunction[6]. It is given in 1 to 1.5 gm. doses every three to four hours for two to six weeks. Regardless of occasional nausea, it may reduce stools, fever, abdominal pain and hematochezia within one week. Complicating sulfapyridine crystaluria, with renal colic and skin eruptions, have occurred.

Although the mechanism of action is not known, ACTH and corticosteroids may protect, as an asbestos suit, from the fires of inflammation[15]. Therefore cells may be guarded but the etiologic agent is unaffected. According to Kirsner these hormones surpass response to any other medical procedure[26]. Indications are anorexia, depression, fulmination, pre- and postoperative care and complications, as *erythema nodosum*, iritis and arthritis. Early vascular inflammation responds much better than later fibrosis and thickening. Consequently, a second course is less effective. Twenty to 30 units of ACTH suspension is given intramuscularly or intravenously twice or thrice daily. Corticosteroids are only 70 per cent effective as ACTH, though a change can be made on the basis of 1 mg. of prednisone as equivalent to one unit of ACTH.

Remissions may be maintained for long periods with oral steroids. Although fever, tachycardia, abdominal discomfort, hematochezia, anorexia and diarrhea subside, proctoscopic improvement is much slower. Radiologic evidence of healing, except disappearance of ulceration, is not to be expected for years. Cushing's syndrome appeared in majority of Kirsner's series, though not so significant as to discontinue therapy. Transient psychoses occurred with one per cent suicides. Allergy to ACTH was found in four per cent and severe infections in two per cent. Giant ulcers healed, massive hemorrhage stopped and nine known peptic ulcers were not reactivated during treatment. Surgical and mortality rates were reduced.

Definitive surgical therapy of total colectomy and mucocutaneous ileostomy is regarded by many as a positive treatment more frequently indicated than performed. Simple ileostomy without colectomy exposes patient to all possible complications and recurrence rate of later re-anastomosis exceeds 50 per cent[21]. Absolute indications for surgery are stricture, perforation, carcinoma and perirectal abscess or fistula. Relative indications are fulminant course after four weeks of medical regime, massive hemorrhage with hypotension, and

unresponsive complications, as arthritis, uveitis and pyoderma. Chronic invalidism, defined as two or more hospitalizations per year over two or three years, is also treated surgically by many. It is best for such a patient to express his desire for ileostomy. Although surgery may effect a cure, ileostomy is a substitution of a lesser disability for a greater. Hence Bargen has stated that chronic invalidism is not a good indication[15].

Prognosis

When prognosticating results of medical or surgical therapies we must heed the experiences of senior gastroenterologists who state that healing of diseased bowel requires months and probably years[15,22,26]. The potentiality of healing is greater than appreciated, and justifies prolonged medical management in absence of serious complications. There are few diseases with such exhaustion and emaciation that recover[23]. In the presteroid era Bargen, Crohn and others independently reported that 75 per cent slowly recover and return to productive occupations, leaving less than 10 per cent mortality, and need for surgery in only 10 per cent[1]. Svartz[6] and Morrison[27] independently stated that azulfidine returned 84 and 70 per cent, respectively, to gainful lives. These results compare favorably with those of Kirsner after ACTH and steroids in which 85 per cent did well, although 70 per cent relapsed, 11 per cent required surgery and 5 per cent died[26]. A statistical "sameness" of various medical regimes is apparent.

The mortality rate of acute fulminating disease is now less than 30 per cent with medical care and 50 per cent with emergency surgery[18,24]. Ileostomy and total colectomy for a good-risk patient has a mortality rate of about 5.5 per cent[21]. Bargen, however, states that 46 per cent of ileostomies may obstruct, though 14 per cent do well[15]. Enteritis, prolapse, stenosis, fistulas, adhesions and retraction required surgical revision in 43 per cent. Such procedures were performed 2.5 times on 73 per cent of complicated ileostomies. Impotence may also occur following abdominoperineal resection.

Wheelock and Warren's analysis of 343 cases followed 10 to 38 years revealed that about 45 per cent underwent surgery and 58 per cent of these within three years of onset. Seventy-nine per cent medical and 94 per cent surgical patients did well, whereas 18 per cent medical and 4 per cent surgical made partial recoveries. Mortality of ileostomy dropped from 27 per cent between 1930-39 to less than 8 per cent from 1950 to 1953. Intestinal obstruction occurred in 21 of 26 patients who underwent surgery[28].

Longevity studies on 1,564 patients by Bargen revealed that there is a 14 per cent less chance of normal survival over 10 years and 22 per cent less chance over 25 years of patients under 50 years of age at time of diagnosis. Carcinoma was found to occur 30 times more often than in general population of similar age. But since a patient 31 years of age has a 58 per cent chance of living 25

years and only a 2 per cent chance of carcinoma, early colectomy did not seem advisable[29]. Contrariwise, we heed Wheelock's report that six patients with cancer after 10 years were not symptomatic enough to need hospitalization[28]. The longer survival of more patients from improved medical and surgical regimes has, of course, allowed more carcinoma to develop.

Conclusion

Actually, when proper medical and surgical therapies are compared, there is little reported difference in results. This speaks well for the selection of patients. All experienced management consists of individualization.

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SURGICAL CURE OF ULCERATIVE COLITIS*

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We were sitting at lunch this noon talking about how Khrushchev said, "You have good farms, and we have better farms; you have good factories but we have better factories", and it reminded us of the "My father can lick your father" attitude of some people. Bill Mortinson, here in the audience, our Santa Monica wit, said that one little Hollywood child came up to another and said, "My father can lick your father", and the second child said, "What are you saying? My father IS your father". (Laughter)

At the outset, one must emphasize that ulcerative colitis is no longer a common surgical disease, and not many surgeons have a wide experience with this disease. And not all who operate on ulcerative colitis have had adequate experience, nor are they abreast of the modern developments, particularly of the last five to seven years.

Coupled with the good, modern medical care which we have heard so ably described this afternoon, fewer patients are coming to surgery, probably in our experience mostly because of the use of steroids and, most of all, Azulfidine.

I think many medical men, and particularly some of the older ones, have been conditioned by bad surgical results in past years in ulcerative colitis, and so I think this has conditioned them to withhold unjustly surgery from people who should have surgery, and keep them in a bondage of economic and physical and mental cachexia. I would like to illustrate a few of these situations that I have inherited.

(Slide) This is a man that I inherited. He has several things which would cause some shock to a gastroenterologist or internist. First, he has a terrific prolapse. He can't wear a satisfactory appliance to keep free from odor or leakage; and furthermore, which is worse yet, he still has his colon. As you see, the mark on his abdomen is the location of a proposed ileostomy and a colectomy to be done in one stage.

(Slide) This is the gentleman's colon. You see here the completely destroyed length of the colon and cecum, including the rectum. He is a chief artist for an aircraft plant, and he has not missed a day's work since he recovered from surgery back in 1954.

(Slide) Here is an unfortunate patient that I also inherited who has several glaring, what we might call "misadventures".

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First of all, she has a transverse incision, something which should never be made in the abdomen for anything except possibly acute appendicitis. The ileostomy is partially contracted; it lies in a groove. She can't possibly wear a bag. She lay in a hospital here in Los Angeles for four months with a suction tube on her abdomen removing all of her ileal content. Not only that; her colon was still in, and when you leave the colon in you are not only predisposed to carcinoma but you contribute to arthritis and all other complications.

(Slide) You all recognize this as a *pyoderma gangrenosum* of the leg.

(Slide) Here is a cameraman from a film studio. Fifteen inches of the terminal ileum is prolapsed permanently. This is a distressing situation. He lay in a hospital for four months, and they had this prolapsed ileostomy draining into a clear plastic bag; so, he could lie there all day and contemplate the gyrations of this horrible monster.

(Slide) Here is his colon, which had been left in. As you see, the disease completely contracted and destroyed the colon.

On the other hand, however, as I said, needless delay will keep people in a state that is no better than this.

(Slide) This next patient whose film you see here was kept out of surgery for 17 years because there was no shortening in his colon. I have felt for years that the term "lead pipe" and "shortening" should be taken out of the radiologist's vocabulary, and I was pleased to hear Dr. Brown studiously avoiding such simple classifications of these people with their complex illness.

This man spent $100 a month for years for doctor bills and medication. He was never able to work or hold a job more than a few months at a time. He was denied surgery because his gastroenterologist said, "You have a good colon. There is no shortening".

(Slide) Here is his colon: Complete involvement with ulcerative colitis from rectum to the ileocecal valve.

He now works for the City of Los Angeles. You saw the date of surgery—1954. I saw him as recently as two weeks ago, and he has never missed a day's work.

There is another type of injustice that comes about in the treatment of ulcerative colitis, and this is patient delay, sometimes through fear, sometimes because a friend will say, "Ileostomy is a living death", or "I would rather be dead than having that thing sticking out of my side with my bowels moving into my pocket".

(Slide) Here is the colon of a doctor's wife. She had up to 35 stools a day for 15 years. During this time she was almost completely invalided. This is an amazing colon. On your lower left is a terminal ileum; on your right is the

sigmoid. Here is a colon shortened up to about 15 or 20 inches from almost 20 years of completely debilitating and unnecessarily tolerated disease.

In past years many of you remember that surgery was greatly feared in ulcerative colitis. It was considered a last resort, and people were never sent to a surgeon until they were completely hopeless. But actually, now, with surgery, these people who undergo it are completely restored to health. And, what is more, these people can eat anything they want that can be chewed.

Why do we have this improvement in surgical results? Because we have better preoperative preparation, we have improved ileostomies and better appliances. Also, we now use ileorectal anastomosis wherever possible and spare the rectal sphincter which, should such loss occur to you and me, we would think is quite important.

We have the application of group therapy for these people in the Ileostomy Association, where they can get a tremendous amount of peace of mind and a good adjustment to their ileostomy; and finally, we preserve their sex function in the male and in the female.

In the preoperative state we have learned that when a sick, chronically ill ulcerative colitis patient comes up for surgery and has a hemoglobin of 80 per cent, we don't consider that patient in good condition. With radioactive iodine-tagged serum albumin—we have found in blood volume studies that these people have a blood volume about 30 per cent of normal. We give them four or five transfusions before surgery, and if you want to meet obstruction, you should try to get that much blood out of the blood bank when you have an initial hemoglobin of 80 per cent. They don't understand that this is a matter of seriously reduced blood volume. You must correct this. We have never found that we give too much.

We now classify conservative surgery as the total one-stage removal of the colon and the creation of an ileostomy, and we call radical surgery the institution of a diversionary ileostomy which leaves the patient still acutely ill, still in a dangerous condition; and, of course, in preserving the colon you have allowed yourself all of the complications that come such as arthritis, carcinoma, and so on.

Fortunately, in the last few years the advent of ileorectostomy has been a wonderful thing to restrain those surgeons who immediately practiced total proctocolectomy for the sick patient in ulcerative colitis. Two things are required: One, you must have a good sphincter mechanism; and second, you ought to have minimal stricture in the rectal segment.

Mr. Stanley Aylette came here two years ago from England and he reported over 100 consecutive cases of ileorectal anastomosis with amazing results, good control and so on. This seems like a brand new thing, but actually Mr. Aylette

had timidly reported a case or two in 1946, and had not met with much enthusiasm, so he rather lost his enthusiasm. Now he has a record of over 100 cases.

The Mayo Clinic up to 1953 had done 30 ileorectal anastomoses where, in very carefully selected cases, they felt the rectum was good enough to be preserved. What happened to the 30 cases? Out of 25 they followed, two or three had to have a terminal ileostomy and the rectum removed; a couple died, but 20 of them are in good condition with good normal functional anal ring.

Dr. Rupert Turnbull, at the Cleveland Clinic, has now done 18 of these cases. In a letter I received from him last week he states he thinks maybe two-thirds of them are going to have good results.

The ability to save the rectum depends on the fact that the terminal two-thirds of the rectum has a different nerve supply from the rest of the colon and the upper rectum. If you have done an ileorectostomy and given the patient a chance to have the rectum preserved and then it fails, you can then go ahead later and remove the rectum and give the patient a modern ileostomy.

Dr. Turnbull introduced the turning back of the outer mucosa over the projecting ileostomy, and this is a most important advance in ileostomy surgery in many years. We can put the bag on in three days and have the patient up and around. We have no problems. We never dilate these ileostomies. If they are made properly, they work right from the beginning.

One of the errors in surgical literature that has been carried from one book to another is that in doing a colectomy you should select a point six inches from the ileocecal valve for division of the ileum and then go ahead and remove the colon. This sacrificing of the terminal six inches of the ileum is horrifying. Here is a water extractor, an electrolyte balancer, which is thrown away with the specimen of colon. We take the ileum off at the ileocecal valve and preserve this vital segment.

Now then, I mentioned this group therapy business. I don't know what towns you come from, but if you don't have an Ileostomy Association in your town, even if it is so small you have only three or four patients, you should have one. Back in 1949 I had the pleasure, and I think now in retrospect although it was painful in some ways, the honor of founding the Los Angeles Ileostomy Association with four of my patients. We had a slow beginning, because one can't go out and advertise the purpose of the association, to have the members call on other patients who need ileostomy and who refuse ileostomy when it is necessary to save their lives.

We did grow definitely in size and in wisdom, and being as tactful as possible, we had publicity through the County Medical Association, so that now anyone who has a seriously ill patient who needs ileostomy, or a patient who has had one who feels totally lost and socially outcast, can call on the Ileostomy

Association and they will visit them, and believe me, gentlemen, they will give them a boost that nothing else can give them. All types of patients can be handled this way, and it is so heart-warming to witness the dramatic results.

Our Los Angeles Association now has about 400 members. We are often spoken of as a child of the New York or Boston organization, but actually we were born at the same time, or I think six months before they were.

Another term in surgical literature that is rather bad for the ileostomy patient: They say, "Do the colectomy and bring the ileostomy out through a stab wound". That's horrible! It may result in badly located and poorly functioning ileostomies—. It is of paramount importance that you know where you are going to locate the stoma.

(Slide) This ileostomy bag that the patient is going to wear is that patient's social security. This is the thing that, if worn properly and cared for properly, makes them totally socially acceptable.

Here is a lovely young lady who has been sick for many years. There is the location of ileostomy marked on the abdominal wall when she is standing before operation.

(Slide) Here is the location of the ileostomy marked when she is sitting.

So we know where this bag is going to be and we know it is going to be comfortable. We know it is not going to leak because it is properly placed.

(Slide) The next slide shows her colon. I think it is an excellent specimen of pseudopolyposis. She had a one-stage proctocolectomy and ileostomy. This was done, as you see, five years ago.

(Slide) Here is a patient with a bag on. This is a long bag which she wears at night and which will hold more liquid.

(Slide) Here is the patient with her clothes on. Certainly there is nothing that is dismaying about having to have such a situation. The bag is not visible.

I want to show you one more patient, because he is a collection of what I would call surgical misadventures.

(Slide) This is a gentleman who came to me, and there are four grave errors in this situation right here. In the first place you see his ileostomy is in the wrong location, right where his belt buckle should be. It is at the most prominent part of the abdomen.

Secondly, he has a transverse incision. I have already mentioned that. These groove very often and you can't wear an appliance. It will not remain cemented to the skin.

Thirdly, it is prolapsed.

Fourthly you see, on the patient, on your left, he has this little bit of ileum implanted there; so, he still has his colon.

(Slide) Here is the patient. He has had a colectomy and here is his new ileostomy.

Now, when you as a surgeon have a fairly large group of ulcerative colitis patients postoperative, you have no problem, and I think it was Dr. Bachrach who wrote a couple of years ago that any gastroenterologist who has three or four seriously sick ulcerative colitis patients has his hands full if he attempts to be both psychological and medical consultant to these patients. As surgeons we can take care of 20 or 30 of them postoperatively with no problem whatsoever. We rarely see them because their complications are really few.

What are the complications? I was amazed when Dr. Brown mentioned the number of re-do's they had at the Mayo Clinic, because that is not our experience. These people do become obstructed, and we have found a severe emotional problem will obstruct an ileostomy. We don't go in there and open the belly and find out what is making the obstruction. We give this patient a tremendous slug of morphine or demerol and disconnect them from their stress situation, put in a catheter, irrigate with saline, and the patient will usually snap right out of it. I don't know of any I have had to operate on except in the immediate postoperative period. Sometimes we get prolapse, but very rarely.

You get a prolapse if you have a patient who wears a belt too tightly and puts too much pressure on the area around the ileostomy, and it will push it out, just as you would expect it to push it out.

You don't like him to lift too much, because excessive lifting will cause your bowel to come out, just like it might cause one's hemorrhoids to fall down.

(Slide) Finally, we do have the complication of spontaneous perforation, and this is a dreaded thing. I can say I have only this one, and this girl got this after an 11-mile hike. She is a swimming teacher, and had been teaching swimming for a couple of years. Fortunately her perforation was in the subcutaneous tissue.

We don't immediately destroy this lovely ileostomy. We drain it on the side, let her establish a small fistula, and about a year later I made a new ileostomy on the other side.

(Slide) Now I can say to you, as they say in the advertisements, "Which one has the Toni?" This group of my ileostomy patients had a barbecue and flattered me by inviting me, and I can say that it was a most heart-warming experience. I know all of these people personally. Only two of the people in this picture do not have ileostomies. There isn't one of these patients who would trade his preoperative state for his postoperative state. Two of these girls have

babies; the rest are competent housewives. The men are all employed, every one of them, and have no illness at all.

And so finally, in closing, what I do want to say is that perhaps in the future, if you medical men would send your ulcerative colitis cases to the surgeon a little sooner, when the rectum is still in good condition, not being traumatized so much from dripdown, not having all of the complications from fistula, fissure and abscess, I think we can save a lot more anal sphincters, and it would be my joy, and mostly the patients' joy, to reduce ileostomy to an almost rare operation.

Discussion

Dr. Clarence J. Berne:—There is one written question that has been addressed to Dr. Hauch. "Will you please discuss the implications of steroid administration in ulcerative colitis with colonic bleeding as compared with steroids with bleeding in the upper gastrointestinal tract. Is any antiulcer regime used in the former?"

Dr. Edward W. Hauch:—There seems to be less gastrointestinal ulceration while patients are on steroids for bronchial asthma or gastrointestinal disturbances (as colitis) than when receiving steroids for rheumatoid arthritis or *lupus erythematosus.* We don't know why. Unsuccessful efforts have been made to determine whether the gastric mucus barrier was permeated in patients receiving steroids. Kirsner's series, already quoted, was remarkably free of duodenal ulceration. Their nine patients with old duodenal ulcers remained quiescent during steroid therapy.

We prescribe an ulcer-type regimen with antacids. Patients whom we feel are adversely affected by milk are advised not to use it, even though receiving steroids.

Dr. Berne:—A second question for Dr. Hauch: "What is your regimen of treatment with ulcerative colitis patients during remission regarding diet, work environment, frequency of follow-up and x-ray of colon?"

Dr. Hauch:—The diet is composed of 3,000 to 3,500 calories and 150 gm. protein with a palatable proportion of carbohydrate to fat. Patients are advised to work on a regular daily schedule, avoiding night shifts. A mid-day rest is desirable if feasible. We prefer to see patients monthly. The large bowel is studied by x-ray every six months if there is activity, and every 12 months during quiescence.

Dr. Berne:—Dr. Boehme, we have a question addressed to you: "Is terminal preservation of the ileum practicable?"

Dr. Earl J. Boehme:—I take it that you mean when there is an ileorectal anastomosis.

My experience isn't as great as that of other people, but there is a little inflammation that occurs in the terminal ileum, but this clears up. There is a moderate stricturing of the ileorectal anastomosis. If you just wait, the patient starts out with sometimes 20 stools a day, and finally in a couple of months they will be down to 5 stools a day and ultimately even as few as two or three.

I don't think the question of ileitis is a worry whatsoever. I think when your ileum is involved you have a combined disease which you couldn't recognize before operation.

Dr. Berne:—I would just like to comment very briefly.

One minor point in regard to patients who are considered to be very sick, and I think I have seen this a number of times: A patient who has extensive major ulceration and weeping of the ulcers of the bowel. An attempt will be made by oral administration to rehabilitate, and this turns out to be a considerable problem, and the reason, or possible explanation, is that the hypoalbuminemia requires that the liver cells do the job of protein synthesis and they are themselves suffering protein deficiency. That which is lacking is serum albumin, and I think it is amazing how in some instances these people, given serum albumin intravenously, will then rehabilitate themselves when they can synthesize amino acids available from ingested food.

Now, with regard to what Dr. Boehme said about ileostomy, I think that maybe we have got to point out this particular fact, that when a patient is years away from his colectomy and he has an ileostomy, his status as an individual, so far as he is concerned, is strictly related to his ileostomy, and if his ileostomy constitutes a disease he is an unsatisfied patient. If the ileostomy is satisfactory, then he has forgotten about his disease and the patient is a rehabilitated individual.

Therefore ultimately satisfaction with the operation is quantitated in terms of the satisfaction in relation to the ileostomy.

I would like to underwrite what Dr. Boehme said in a very gracious way, which is that in recent years a great deal has been learned and that tremendous progress has been made in the operation of ileostomy. This may be hard for people who don't work with this problem to realize, but it is known today by those who know how to do an ileostomy, so that it is a tremendously different situation in the recovered patients than it used to be just a few years ago.

I, too, was shocked by some of the statistics with regard to trouble from ileostomy. This is casting back into surgical history, in the era of evolution of ileostomy, and the ability of surgeons to know how to do ileostomy. It is something you wouldn't believe was true relative to the last 15 or 20 years, to know what things were like then and what they can be like now.

I would like also to emphasize that perhaps one of the most fortunate things that can be done for ileostomy candidates is for them to see an ileostomy patient, have the person come and sit and talk with them. This, I think, is one of the most important things that I know. It gives comfort and assurance and satisfaction to the preoperative patient.

Dr. Bauer, would you care to say anything?

Dr. Julius Bauer:—Simply a few words, that if you were as an impartial listener this afternoon to summarize what we learned for practical purposes, we would say first it would be good to follow the regime of Dr. Rowe and, as a matter of fact, that would suffice. If it works, then we don't need the surgeon. If it doesn't work, then we have to turn to the surgeon. That is quite clear.

I want to mention another point which was not mentioned today, and I think it is rather important. That amebic dysentery is an acute specific infectious disease is known, but it happens that these people who were cured of their amebic dysentery are still getting antiamebic treatment although it is not amebic dysentery any more but ulcerative colitis. I remember a particular case of a student who acquired the disease in Mexico some 15 years ago and was properly treated and never had amebae any more, on many examinations here and in the East, but he still was treated for amebic dysentery when he had diarrhea due to ulcerative colitis.

This is wrong. I think there is an allergic manifestation which may be initiated by some known material or other infectious agent, and I think that should be kept in mind. Ulcerative colitis is the type of colitis where we don't find any specific virus or material or microorganism.

CLINICAL EVALUATION OF DESITIN OINTMENT AS A PERISTOMAL MEDICATION

JEROME WEISS, M.D., F.A.C.G.

New York, N. Y.

The postsurgical problems for the patient with an ileostomy or colostomy are indeed numerous. Perhaps the most serious of these is the psychological trauma accompanying the procedure itself and the subsequent adjustment required for this new way of life. If the patient has great difficulty in making the many adjustments, his physical well being will of course suffer. Simultaneously the reverse situation also holds true. For as long as the area involved is subject to peristomal edema, excoriation, with its accompanying itching and burning, and scattered areas of recurrent skin breakdown there can be no psychological peace nor proper adjustment to the abrupt disruption of normal physiological processes.

There are several factors that have been suggested as being the causative agents for the peristomal difficulties. Some have said that the degree of fluidity of the stomal discharge is to blame, others claim that it has to do with the pH of the residue, still others feel that the remaining enzymatic activity in the incompletely digested food is at fault, while there are some who hold that the general nutritional status of the patient is a prime factor. There can be no dispute that logically any or all these reasons are contributory to the general discomfort which usually is present, and steps must be taken on a general basis to correct them all. Once, however, irritation, excoriation, erosion and skin sloughing has occurred it persists chronically despite the corrective steps taken to eliminate most etiological causes. Most of the irritation occurs during the first 6 weeks after operation. It therefore becomes necessary to protect the surrounding skin areas from further breakdown, as well as soothing the already affected areas, and promoting healing in a most efficient manner, while correcting the other features.

Method of Study

Having had indifferent success in the past while using a variety of creams, lotions, pastes, powders, and other materials it was decided to seek the most efficient combination of products by doing a controlled study on a small group of ileostomy and colostomy patients, including those who had recently undergone surgery as well as those who had been subjected to recurrences of peristomal irritation for various periods of time. All of them had some degree of excoriation or skin breakdown, with pain, burning or itching as major complaints.

The materials used in this study were:

1. Boric acid ointment

2. Vaseline
3. Aluminum paste
4. Zinc oxide
5. A combination of

   Cod liver oil

   Zinc oxide

   Talcum

   Petrolatum

   Lanum

   (Desitin Ointment)

Each of 11 consecutive patients were treated with a consecutive cycle consisting of three days each, of all the various materials in a different successive order.

Daily records were kept of changes in both subjective and objective symptoms during the entire course of treatment with special note made of the following: irritability; appetite; soreness; itching; burning; redness; swelling; weeping or erosion of the skin; stomal activity; sleep.

Observations

It was observed in all 11 of the recorded cases that the progressive improvement of the involved skin area was at the same rate no matter what the order of succession of the materials were, except that definitely less improvement was noted during the time that Vaseline was used in the early stages. After the 9th day, the Vaseline did not adversely affect the rate of progress observed in the healing.

It was felt that each of the individual items other than Vaseline, when applied regularly and with care, exerted a definite influence in producing regression of the peristomal edema, excoriation, and skin breakdown with relief of the accompanying pain, burning and itching as well as showing improvement in the psyche, appetite and nutrition of the patient. It was also noted that the combination of ingredients (Desitin Ointment) caused the most rapid relief from the itching, burning and pain in the early stages.

The time for the complete healing of the involved area varied between 15 and 26 days, with the average time being 19 days, provided there were no intermittent periods of upper respiratory disease, gastroenteritis or severe psychic trauma which would influence the fluidity of the discharge. The earliest time

for complete healing was in those cases where the cod liver oil combination was used as one of the first three applications.

Summary

Eleven consecutive patients with ileostomy or colostomy who showed evidence of peristomal irritation were carefully observed while being treated with a varied succession of five specific ointments or pastes. All showed improvement in an average of 19 days, except that the cod liver oil ointment (Desitin) produced healing within 15 days. Those patients who received Vaseline during the early stages showed slightly slower progress in healing in the beginning, but when it was used later in the course of treatment, the progress was adequate. A combination of ingredients (Desitin Ointment) produced the most marked subjective relief of itching, burning and pain, symptoms which were most annoying during the early stages of treatment.

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In Memoriam

We record with profound sorrow the passing of Dr. Felix Cunha, San Francisco, Calif., Fellow and Dr. Roman R. Perkul, New York, N. Y., Member of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

ABSTRACTS FOR GASTROENTEROLOGISTS

ESOPHAGUS

ACHALASIA OF THE ESOPHAGUS WITH PULSION DIVERTICULUM: William J. Pickett and W. M. Moss. Illinois M. J. 115:17 (Jan.), 1959.

Sweet describes two types of achalasia, both being characterized by absence of Auerbach's ganglion cells. Type I achalasia which accounts for 80 per cent of the total, is characterized by excessive dilatation of the esophagus with an atrophic lower segment and absence of pain, spasm or peristaltic activity. Type II achalasia accounts for the remainder of 20 per cent, characterized by less dilatation of the esophagus and hypertrophy of the circular muscle layer of the lower segment and presence of substernal pain with spasm. Radiographic examination of type II achalasia reveals active but abnormal peristalsis.

JOSEPH E. WALTHER

ACHALASIA OF CARDIA, CARCINOMA OF ESOPHAGUS, AND HYPERTROPHIC PULMONARY OSTEOARTHROPATHY: M. A. Peyman. Brit. M. J. 5113:23 (3 Jan.), 1959.

This case report documents the development of carcinoma of the middle third of esophagus in a 49-year old man with known achalasia of the esophagus of 23 years' duration, self-treated with daily mercury bougie. Symptoms consisted of severe dysphagia, which responded to further bougie treatment, weight loss, and pain and swelling in the ankles, knees, wrists, and finger joints. X-ray examination of these regions showed hypertrophic pulmonary osteoarthropathy. Esophagram showed filling defect in the middle third but diagnosis was not established until esophagoscopy was performed after a fortnight of lavages. Thoracotomy showed that the growth had spread into both hilar regions and was involving the pleura as well as becoming firmly attached to the aorta and vertebral bodies. Chronic irritation as a cause of malignant degeneration is discussed.

ERNEST LEHMAN

STOMACH

CAUSE OF PEPTIC ULCER: Lester R. Dragstedt. J.A.M.A. 169:203 (17 Jan.), 1959.

There is no proof that peptic ulcer is due to a local decrease in the resistance of the mucosa to the digestant of the gastric content. However, pure gastric juice is able

to digest all living tissue and may produce a defect resembling peptic ulcer. Patients who secrete large volumes of gastric juice are unable to obtain the neutralizing effect of food and alkalis. This hypersecretion is of nervous origin in duodenal ulcer, whereas, the hypersecretion of gastric ulcer is usual humoral or hormonal in origin. Gastrojejunal ulcers develop from low gastric resection for duodenal ulcer, because the cause of hypersecretion is nervous and is not corrected by excision of the gastric antrum. The removal of the antrum usually abolishes the cause of hypersecretion and thus gets a low incidence of gastrojejunal ulcer. Patients with duodenal ulcer have from 3-20 times the normal amount of HCl in the fasting stomach at night. Cutting the vagal nerve reduces the nocturnal fasting secretion and when combined with gastroenterostomy so as to prevent stasis of food in the pyloric antrum the duodenal ulcer heals and remains healed. This was demonstrated in 500 patients. Gastric ulcer on the other hand, occurs in patients whose stomach is atonic and shows a fasting secretion less than normal. Stasis of food in the stomach causes excessive secretion of humoral origin and then formation of ulcer which is relieved by gastroenterostomy. Measurement of nocturnal fasting gastric acid is of great value in deciding whether vagotomy combined with antrum resection or gastric resection alone should be done for gastric ulcer.

The author then goes into great detail as to the operation for duodenal ulcer, preoperative preparation, type anesthesia, and actual operative procedure, with careful postoperative care and follow-up studies in these patients.

LOUIS K. MORGANSTEIN

PEPTIC ULCER AND OTHER GASTROINTESTINAL DISORDERS: TREATMENT WITH A NEW ANTIPHOBIC-SPASMOLYTIC-ANTACID COMBINATION: Louis A. Rosenblum. Clin. Med. 6:73 (Jan.), 1959.

The rationale for the use of this new combination of drugs, antiphobic, spasmolytic and antacid is given and cases reported to cite the efficacy of the mixture. Additional reports should be forthcoming; the reasons given for the therapeutic trial of the ingredients are good.

IRVIN DEUTSCH

PYLORIC CHANNEL ULCER: Richard L. Whittaker and Alvin J. Cummins. Am. Pract. & Digest. Treat. 10:72 (Jan.), 1959.

The purpose of this paper is to emphasize the occurrence of pyloric channel ulcer and in particular to stress the more important features of this condition. Because the clinical picture can be so atypical of peptic ulcer disease as it is usually seen, delay in diagnosis and therapy can occur.

The usual manifestations are nausea and vomiting, atypical abdominal pain, and a shorter, stormier course than that usually seen in ulcer disease. Pyloric obstruction is a common feature.

Demonstration of an ulcer niche or crater is essential for the absolute diagnosis. Other roentgenologic features of the condition are discussed.

The treatment of pyloric channel ulcer differs from that of ordinary peptic ulcer disease only in degree. These patients should be hospitalized and placed on a vigorous medical regime. As with peptic ulcer disease in other sites, free perforation, hemorrhage, and posterior penetration into the pancreas may occur.

Four cases of pyloric channel ulcer are presented in the paper. In two cases the patient experienced recurrence of ulceration in the same location as seen in the first examination.

I. HENRY EINSEL

TREATMENT FOR PERFORATED PEPTIC ULCER: Carl A. Gherardi and Francesco Baldrati. J. Internat. Coll. Surgeons 31:154 (Feb.), 1959.

This is a report on the treatment of 181 perforated peptic ulcers. The opinion of the authors is that simple closure of the perforation is the best method of therapy and that more extensive surgical procedures during the acute perforation stage is not to

be condoned as the method of preference. Conservatism is advocated only when the clinical picture plus x-ray evidence clearly indicates or suggests that the perforation is closed or has been closed spontaneously.

BERNARD J. FICARRA

GIANT INNOCENT GASTRIC ULCER: S. L. Strange. Brit. M. J. 5120:476 (21 Feb.), 1959.

The term giant gastric ulcer is restricted to defects with a diameter of more than 3 cm. occurring on the lesser curvature of the stomach between the angulus and the cardia.

In a series of 73 cases, 47 males, 26 females, 71 ulcers were found to be non-malignant.

Pain was predominating symptom in 70 cases, hemorrhage occurred in 25 instances, perforation in 3.

Emergency surgery was performed on 21 of the hemorrhage cases with a mortality of 7.

Fifty-two cases were placed on medical treatment with a view to elective surgery at a later date.

Elective surgery was done early in 13 cases because of gastric retention, uncertainty of character of lesion or because of long ulcer history.

A further 21 were operated upon because of partial healing under medical therapy or of recurrence after healing.

Eight patients, 5 males and 3 females have remained cured after medical treatment for a period of 2 to 5 years.

The results of this study seem to indicate that surgery is needed for extirpation of large gastric ulcers, 77 per cent of the total required this and of the 36 treated medically only 8 responded favorably.

J. EDWARD BROWN

INTESTINES

INTESTINAL PERFORATION AND WIDESPREAD ARTERITIS IN RHEUMATOID ARTHRITIS DURING TREATMENT WITH CORTISONE: R. A. Parker and Phyllis M. Thomas. Brit. M. J. 5121:540 (28 Feb.), 1959.

Three cases of intestinal perforation and of widespread arteritis in the course of cortisone treatment of rheumatoid arthritis are presented. It is worthy of note that all three were males of 54, 45, and 39 years of age respectively. All three contracted their intestinal perforations at places not affected by preexisting pathology. All three cases had a fatal outcome caused by generalized peritonitis despite timely laparotomies. The sites of perforation were jejunum, cecum, and sigmoid respectively. At autopsy all three cases showed widespread acute arteritis with fibrinoid necrosis. Widespread arteritis of the acute type is rarely found in rheumatoid arthritis, but since the advent of cortisone therapy such cases appear to have increased. The authors conclude "Cases of rheumatoid arthritis if treated with cortisone are more liable to develop acute arteritis" which in turn may lead to intestinal perforation at sites not affected by preexisting pathology. The authors believe that all three cases of intestinal perforation and of widespread acute arteritis represent abnormal reactions to cortisone which are more likely to occur in cases of rheumatoid arthritis than in other diseases.

WALTER CANE

INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT: J. Eugene Lewis, Jr. Missouri Med. 56:141 (Feb.), 1959.

Meticulous details for differential diagnosis are presented by the author. He stresses the importance of physical examination at birth and of close observation for the first 24 hours. Anal inspection and rectal digital examination as well as gastric aspiration with an urethral catheter should be done at the slightest sign or suspicion. Vomiting of bile-stained material by a full term infant is invariably associated with

intestinal obstruction. Failure of the newborn to pass meconium after 12 hours is a warning signal, after 24 hours it becomes a danger signal. To rule out a diagnosis of intestinal obstruction without radiographic examination is presumptuous. To make the diagnosis by radiographic examination alone is irresponsible. A dilute contrast enema is important for obtaining clear information about the colon as to outline, position, and patency. Without a contrast enema, the radiologist cannot clearly differentiate between small bowel and large bowel obstruction. Four cardinal manifestations of intestinal obstruction in the newborn are maternal polyhydramnios, green vomitus, abdominal distention, and abnormal evacuation of meconium. At operation patency of the bowel must be ascertained in order to eliminate multiple anomalies. In addition gastrostomy is recommended. the catheter being invaluable for postoperative decompression and for supplementary feedings. Gastrostomy is mandatory in premature infants.

WALTER CANE

SURGERY—CARCINOIDS, THE MALIGNANT CARCINOID SYNDROME AND 5-HYDROXYTRYPTAMINE (SEROTONIN): Gerald W. Peskin and Marshall J. Orloff. Am. J. M. Sc. 237:224-237 (Feb.), 1959.

In the article regarding Progress of Medical Science, the authors describe the historical aspects, incidence, malignant potential, the sites of origin, pathology, pathogenesis, and the various aspects that make the carcinoids the type tumor, and cause it to produce the variety of symptoms, one has learned to expect. The action of serotonin is described. Treatment is discussed, particularly as related to surgery and the use of serotonin antagonists. At the present time, no adequate antagonist has been found. Symptomatic and palliative measures are discussed.

BERNARD FARFEL

METASTATIC CANCER OF THE SMALL INTESTINE (WITH SPECIAL REFERENCE TO A CASE OF EPITHELIOMA OF THE SMALL INTESTINE SECONDARY TO AN EPITHELIOMA OF THE BRONCHUS): M. Conte, Mme. Conte-Marti, P. Baledent and C. Frelot. La Semaine des Hopitaux, p. 461 (12 Feb.), 1959.

In a 49-year old man the only clinical sign of a secondary epithelioma of the small intestine was melena occurring four months after the patient had sustained a pneumonectomy for a left bronchial epithelioma followed by death within three weeks.

Postmortem showed metastases in both adrenals, in the liver and small intestine, of the same histological type as that of the primary bronchial epithelioma.

There are only 55 cases of secondary tumor of the small intestine reported in the literature.

The primary tumor was often an epithelioma of the cervix uteri (18 per cent of the cases) or a malignant melanoma (18 per cent); a bronchial origin was found only in 2 cases, of which the one is reported here. The small intestine was probably involved by the circulation way.

On the whole, the usual symptomatology is that of an incomplete occlusion of the small intestine, the hemorrhage being (as in the present case) pretty rare. In 31 cases the radiologic examination of the small intestine was performed, it allowed in 18 cases an accurate diagnosis which would otherwise have been possible only on surgical intervention or on postmortem.

INTERMITTENT VOLVULUS OF THE RIGHT COLON: J. A. Barss, J. J. Coury, D. A. Koch, E. C. Sites and H. J. Hazeldine. Am. J. Surg. 97:316 (Mar.), 1959.

The authors deal with cases of partial obstruction, due to abnormal fixation and mobility of the colon, which spontaneously reduce themselves. A report of 38 cases is given and in the majority the symptoms were: sharp, localized cramping pain in the right lower quadrant, lasting from one to several hours. Nausea and anorexia were rather common during attacks, but fever and vomiting were characteristically absent. These symptoms persisted intermittently for months or years. During attacks, tenderness

in the right lower quadrant was common, but laboratory findings were within the normal or near normal range in all patients. Barium enema was most useful in ruling out other conditions of the colon but did not contribute directly to the diagnosis. The chief problem in most patients studied was in differentiating cecocolic torsion from acute or recurrent appendicitis.

At operation, the right colon was usually found to be very loosely attached by a filmy peritoneal membrane to the lateral wall, and freely movable. The surgical procedure is reported and includes suturing the colon into a normal position against the peritoneum in the lateral gutter. An incidental appendectomy was also performed, if not previously done. The results of surgical correction were satisfactory. All patients were relieved of pain.

CARL J. DEPRIZIO

CARCINOMA OF THE ILEUM OCCURRING IN AN AREA OF REGIONAL ENTERITIS: Major David P. Buchanan Capt. Gilbert D. Huebner, Capt. Samuel C. Woolvin, Capt. Robert I. North and Capt. Trevor D. Novack. Am. J. Surg. 97:336 (Mar.), 1959.

The occurrence of adenocarcinoma in an area of small bowel involved in regional enteritis is so rare as to merit presentation. A case report is given of a 47-year old white male, with a history of regional enteritis for 28 years: he was operated upon and carcinoma of the ileum was found. The pathological report is given in detail.

The gradual merging of inflammatory and neoplastic elements, as well as the presence of metastases in regional lymph nodes leaves no doubt that this actually is such a case. The history of 28 years of loose bowel movements is consistent with long-standing regional enteritis. It is unlikely that adenocarcinoma had been present since the onset of symptoms 28 years ago, or even since the diagnosis of regional enteritis was established in 1955.

CARL J. DEPRIZIO

THE SURGICAL APPROACH TO ULCERATIVE COLITIS: Mark M. Ravitch. Wisconsin M. J. 58:147 (Mar.), 1959.

The author recommends surgical treatment for ulcerative colitis that requires operation. It is suggested that the entire operation, colectomy and abdominoperineal resection all be performed in one stage. There is a lessened risk of one operation, one incision, one anesthesia and the advantage of immediate ablation of the diseased bowel. Indications for total colectomy and abdominoperineal resection were: 1. intractable colonic disease with anemia, diarrhea and debility; 2. massive hemorhage; 3. life threatening fulminating attacks with high fever; 4. long continued disease with severe radiologic deformity. The technic and operative procedure is carefully described.

ABRAHAM BERNSTEIN

LARGE BOWEL OBSTRUCTION DUE TO SLIDING FEMORAL HERNIA: Graham E. Schofield. Scottish M. J. 4:118 (Mar.), 1959.

The author reports a case of intestinal obstruction due to a sliding femoral hernia which contained pelvic colon.

Sliding femoral hernia containing colon is very rare as compared to inguinal hernia. The anatomic proximity of the internal inguinal ring to the colon and the fact that the femoral canal is bounded by relatively unyielding structures are important factors responsible for the infrequency of the type of hernia reported in this article.

THEODORE COHEN

LEIOMYOSARCOMA OF THE ILEUM WITH PERFORATION: James J. Maurer. Ohio M. J. 55:352 (Mar.), 1959.

This is a case report of surgery for an acute abdomen due to perforation of a diverticulum of the ileum with the finding of a leiomyosarcoma in the diverticulum.

The case is reported because of its rarity. It is of interest that the patient had been admitted six years previously for abdominal pain and diarrhea and found to have a severe anemia. He was thought to have an acute duodenal ulcer with hemorrhage at that time.

BERNARD FARFEL

ABDOMINAL ACTINOMYCOSIS: John R. Cummings, Marts E. Beekley and Neal Earley. Ohio M. J. 55:350 (Mar.), 1959.

This is a case report of a 39-year old white male who was under observation on several occasions because of abdominal pain, fever, anorexia, and fatigue. The diagnosis was not made until the finding of a draining sinus tract occurred about one and one half years later. Laboratory technic to determine the diagnosis is described and a description of the therapy employed is included.

BERNARD FARFEL

SURGICAL MANAGEMENT OF ULCERATIVE COLITIS: Rupert B. Turnbull, Jr. J.A.M.A. 169:1025 (7 Mar.), 1959.

In order to alleviate the necessity for permanent ileostomy after colectomy for ulcerative colitis, a modification of Aylett's ileorectal anastomosis procedure is proposed. The indications for colectomy in ulcerative colitis are first reviewed. Colectomy is performed through a left abdominal incision leaving the right abdomen free for ileostomy which is performed with eversion technic and immediate suturing to the skin. Unlike Aylett, the anastomosis is performed a year or more after the primary surgery. At that time, the rectum is mobilized, excising part of the rectum with the sigmoid colon and making an end-to-side anastomosis of the ileum to the remaining rectum. Immediate results consist of frequent defecations, which generally subside. Rectal continence was attained in 13 of the 14 cases operated, but not in one case because of a rectal sphincter damaged by disease. No abscess or fistula formation occurred. Of the 14 patients, four are considered failures, two because of failure to heal the rectal disease, one previously mentioned and one because of ascending ileitis.

STANLEY STARK

SURGICAL TREATMENT OF DIVERTICULITIS OF THE COLON: Carl P. Schlicke and Arch H. Logan. J.A.M.A. 169:1019 (7 Mar.), 1959.

A review of facts relating to diagnosis and treatment of 70 surgically treated cases of diverticulitis of the colon is presented. The clinical picture may be confusing since the picture frequently presents in the shape of a gynecological problem or carcinoma of the intestines. Eighteen patients presented no gastrointestinal symptoms. Gross bleeding occurred in 13. Appendicitis is frequently the preoperative diagnosis. There was no change in bowel habit in 30 per cent of the cases. Leucocytosis is frequently absent, as was fever. Radiographically diverticulosis was easily diagnosed, but diverticulitis was often missed. The indications for surgery were: 1. intractability of symptoms; 2. presence of a palpable mass; 3. inability of radiologist to exclude carcinoma; 4. obstruction; 5. bleeding and 6. external fistula. The surgical procedure of choice was the one stage resection and anastomosis. However, if recognition and treatment are delayed until complications occur, the multiple stage procedures may still be carried out.

STANLEY STARK

LIVER AND BILIARY TRACT

CHOLESTASIS PRODUCED BY THE ADMINISTRATION OF NORETHANDROLONE: F. Schaffner, H. Popper and E. Chesrow. Am. J. Med. 26:249 (Feb.), 1959.

Norethandrolone was administered to 27 patients for three to five weeks. Liver biopsies were performed before and after administration of the drug. Histologic evi-

dence of cholestasis was found in four patients. In each of these instances the SGOT activity increased above 150 units from normal levels. In one patient severe jaundice developed which lasted ten weeks. The remaining patients tolerated the drug well and gained weight. In a control group of 28 patients receiving a tranquilizing drug and similarly studied no instances of cholestasis were found.

Inflammatory reaction in the portal tracts and around proliferated ductules (cholangiolitis) was not associated with the cholestasis although it was present in some patients before and after administration of norethandrolone.

JOHN M. MCMAHON

THE FATTY MEAL IN ORAL CHOLECYSTOGRAPHY: A REEVALUATION, WITH COMMENTS ON "TUMORS" OF THE GALLBLADDER, AND ON ITS ROKITANSKY-ACHOFF SINUSES: Christian V. Cimmino. Am. J. Digest. Dis. 4:159-170 (Feb.), 1959.

The fatty meal was of value in diagnosing noncalculous filling defects in the proximal half of the gallbladder. It was of minimal value in diagnosing stones. Without the fatty meal, a morphologic diagnosis would have been missed in about 1 per cent. The fatty meal was found to be of limited value in the diagonsis of function as a possible manifestation of cholecystitis.

WALTER CANE

TRANSCUTANEOUS HEPATIC CHOLANGIOGRAPHIC STUDY: ITS IMPORTANCE IN THE DIAGNOSIS AND MANAGEMENT OF BILIARY DISEASE: Earl J. Halligan and Ralim Farid. J. Internat. Coll. Surgeons 31:145 (Feb.), 1959.

The differential diagnosis of jaundice is very difficult. One must be able to differentiate between medical and surgical jaundice, and the site and nature of obstruction, in cases of extrahepatic jaundice. The literature on transhepatic cholangiography is carefully reviewed. The authors have performed over 3,000 liver biopsies without complications. Complete discussion on eight cases of obstructive jaundice with operative and postmortem studies of the liver are presented.

The indications for transcutaneous cholangiographic studies are differential diagnosis of jaundice, localization and identification of the lesion, temporary drainage of the biliary system, direct injection of antibiotics into the biliary tree, and measurement, pressure, and metabolic studies of the bile.

ABRAHAM BERNSTEIN

HEPATIC LOBECTOMY: Alexander Brunschwig. Am. J. Surg. 97:148 (Feb.), 1959.

The author reports on 34 lobectomies for varying types of neoplasms; 28 were right hepatic lobectomies and 14 were left hepatic lobectomies. He has never seen a permanent biliary fistula resulting from partial hepatectomy. The cardinal principle of liver surgery is the placing of soft rubber drains to the operative sites to facilitate the escape of bile and blood during the immediate postoperative period. The entire right or left lobe of the liver may be resected. Complete details of the operations are given.

In the series of 34 cases, the operative mortality for simple total right hepatic lobectomy was 36 per cent; complex total right hepatic lobectomy, 85 per cent. This included surgery of the hepatic bile ducts, duodenum and pancreas. Total left hepatic lobectomy mortality was 15 per cent. Diffuse cancerization of the liver or a diffuse form of cirrhosis of the liver, precludes any indication for surgery.

Four patients in the total series are living, more than five years after total right hepatic lobectomy. One patient lived over 17 years following left hepatic lobectomy. This was in conjunction with radical gastrectomy for cancer of the stomach.

Two factors are regarded as especially dangerous in connection with surgery of the liver: 1. Hemorrhage. 2. Infection. If the large blood vessels are clamped and ligated firmly, the weeping of blood from the parenchyma is soon arrested by pressure with dry gauze sponges, or gauze sponges soaked in saline solution.

CARL J. DEPRIZIO

TECHNIC OF CHOLECYSTECTOMY: George Francis Miller. Am. J. Surg. 97:151 (Feb.), 1959.

Acutely diseased gallbladders are often much more easily removed from above down. The basic safeguard of positive identification of all structures by careful dissection, before division or ligation, and strict adherence to this rule will prevent dangerous errors. Most of the difficulties center about the cystic artery, because of the many anatomical variations or anomalies. The cystic duct also presents many problems and one should be aware, especially of the excessive length of the cystic duct that may be adherent to the common duct. Complete dissection of the cystic duct under direct visualization is advocated.

CARL J. DEPRIZIO

ACUTE CHOLECYSTITIS: John J. Byrne. Am. J. Surg. 97:156 (Feb.), 1959.

A series of 134 cases of acute gallbladder disease are reviewed pathologically and clinically. From the pathological point of view there is good evidence that gallbladders may be easily operated upon within the first ten days of an acute attack and that the earlier this is done, the less chance there is for subsequent perforations either by gangrene or infection.

Watchful waiting is difficult since there is a poor correlation between the signs and symptoms and the complications of gallbladder disease. The differential diagnosis should carefully rule out hepatitis, heart disease, pneumonia, pancreatitis and pyelonephritis. Unless there are definite positive indications, exploration of the common duct is not advised, particularly in patients with associated vascular diseases.

The over all mortality rate was 12 per cent and varied with the condition of the gallbladder and physical status of the patient.

CARL J. DEPRIZIO

THE USE OF ADRENAL STEROIDS IN SUBACUTE AND CHRONIC CHOLANGIOLITIC HEPATITIS: Moshe B. Goldgraber and Joseph B. Kirsner. A.M.A. Arch. Int. Med. 103:354 (March), 1959.

Cholangiolitic hepatitis is a syndrome of varied etiology. The virus of infectious and serum hepatitis, various poisonings and medicinal drugs can produce it. Microscopically, it is characterized by inflammation of the bile ducts, obstruction with bile thrombi and cell infiltration around the ducts. Four cases representing this syndrome were observed while under treatment with adrenal steroids. These hormones increased the appetite and the well-being of the patient and produced weight gain. They also reduced the degree of jaundice. However, there was no change of the majority of liver function tests and the liver size. Also the microscopic findings were unaltered as demonstrated by repeated liver biopsy specimens. The serum alkaline phosphatase which is always considerably elevated in this disorder decreased, while at the same time the serum cholesterol increased during therapy. This showed that both substances are independent from each other. *L.E.* cells were found in two patients not showing the microscopic characteristics of lupoid hepatitis. One patient progressed to subacute necrosis, the other to biliary cirrhosis, while under steroid therapy.

H. B. EISENSTADT

CURRENT CONSIDERATIONS OF ACUTE HEPATIC DISEASES: M. C. F. Lindert. Wisconsin M. J. 58:153 (March), 1959.

This paper begins with a discussion of differential diagnosis of acute hepatic disease. It is a good review and worthwhile reading. The discussion of liver involvement is gone into in detail and instances are described when the liver is overlooked despite the presence of jaundice. Five cases of acute hepatic diseases are presented; all these patients were treated for several months to a year, for acute viral disease. The treatment for this condition is generally nonspecific and empirical. A brief description is given regarding the criteria of healing of the acute hepatic disease patient.

ABRAHAM BERNSTEIN

TECHNIC, HAZARDS, AND USEFULNESS OF PERCUTANEOUS SPLENIC PORTOGRAPHY: William F. Panke, Edward G. Bradley, Augusto H. Moreno, Francis F. Ruzicka, Jr. and Louis M. Rousselot. J.A.M.A. 169:1032 (7 March), 1959.

Percutaneous splenic portography is useful in the definite diagnosis of portal hypertension. Extent of extrahepatic collateralization, major vessel size, presence of portal and/or splenic vein thrombosis, and compression or invasion of major portal radicles may be demonstrated. Contraindications consist of marked alterations of the blood clotting mechanism, history of allergy, uncooperative patient, or known tumors of the spleen. All patients are hospitalized and blood clotting mechanisms checked. The patient is carefully instructed in control of respiration. With a fasting patient, previously prepared with neomycin and enemas, the patient is well sedated or anesthetized. Local anesthesia may be given and a test dose of dye is given prior to the procedure. After careful radiographic positioning and with very sterile technics, an 18 gauge spinal needle is introduced into the spleen through the 9th intercostal space in the posterior axillary line. Manometric readings are made at table level and then corrected for position. Dye is then injected (5 c.c.) and studied fluoroscopically for entrance of the dye into the splenic pulp and then 40 c.c. of dye are rapidly injected with films taken at 2, 4, 6, 8, 12, 16, 24, and 32 second intervals by manually shifting the casettes. The patient is checked for vital signs for the next 24 hours and food is limited to fluids until the following morning.

No serious allergic reactions have occurred in 266 examinations. The majority of patients have some pain, occasionally severe. Bleeding requiring transfusions occurred in 4 cases usually when more than two punctures had been made. Infection occurred in 2 per cent of patients, with one patient dying from Welch's bacillus bacteremia. False puncture occurred in 2 per cent of cases, and transitory chemical pleuritis was recognized in two patients. Failure occurred in 8 cases.

STANLEY STARK

LATE PROGNOSIS OF CHLORPROMAZINE JAUNDICE: A. G. Melrose and J. R. Roy. Brit. M. J. 5125:818 (28 March), 1959.

Two patients who had chlorpromazine jaundice six months and one year previously had follow-up liver biopsies and liver function performed. In both cases there were persistent histological changes and in one case the liver function tests remained abnormal.

The incidence of liver reactions (25 per cent) studied by biopsy is higher than the frequency of clinical jaundice (1 per cent) would indicate. Although rare, biliary cirrhosis may follow the clinical jaundice. As a result, the authors recommend careful consideration before using this potentially toxic drug.

THEODORE COHEN

GASTROINTESTINAL TRACT HEMORRHAGE DUE TO GALLBLADDER DISEASE: William M. Stahl, Jr. New England J. Med. 260:471 (5 March), 1959.

The author presents a case of hemobilia which is massive bleeding through the bile ducts into the gastrointestinal tract. The clinical picture was that of sudden onset in a 62-year old female with known gallbladder disease, of acute epigastric and right upper quadrant pain, nausea, vomiting of 500 c.c. of coffee ground material and passage of tarry stool, temperature—104, disorientation and development of obstructive jaundice. She was operated on the 5th hospital day. An inflammatory mass in the gallbladder area was found; the common duct was opened and found to be completely occluded by a well formed clot extending into the hepatic duct system and into the liver substance. The distal clot was removed and contained stones and debris of gallbladder mucosa. The gallbladder contained blood and purulent exudate.

The author has consulted the literature and states that in addition to many reports of hemobilia due to trauma to the liver, there were only 13 authenticated cases, including his own, of nontraumatic origin. The causes include tumors of the liver, gall-

bladder and bile ducts and conditions secondary to inflammatory disease of the gallbladder and ducts. They include acute hemorrhagic cholecystitis, infarction of the gallbladder and ulceration by stones.

SAUL A. SCHWARTZ

PATHOLOGY OF JAUNDICE RESULTING FROM INTRAHEPATIC CHOLESTASIS: Hans Popper and Fenton Schaffner. J.A.M.A. 169:1447 (28 March), 1959.

The authors discuss the following groups: A. Gross and Mechanical Obstruction: 1. Obstruction of the larger intrahepatic bile ducts as by stone, carcinoma, or after operation. Since many parts of the liver can escape, neither jaundice nor biliary cirrhosis are necessarily present. 2. Obstruction of septal bile ducts within the small portal tracts—this includes less common lesions such as Hodgkin's disease, schistosomiasis, leukemia and others; and these need not necessarily be accompanied by jaundice. Of the jaundice group, the most important is the so-called primary biliary cirrhosis in older women. Hanot's cirrhosis belongs in this group. 3. Periportal ductular obstruction—In this group belongs jaundice after the relief of extrahepatic obstruction, as for example in gallstones. The end stage of the above lesions is biliary cirrhosis. In general, the group includes prolonged cholestasis of intra- and extrahepatic origin.

B. Intrahepatic cholestasis without tangible mechanical obstruction. The degree of jaundice is not directly related to the degree of hepatocellular damage. 1. Cholestasis is present in hepatic disease. It may be present in large fatty livers with jaundice; diffuse septal cirrhosis; postnecrotic cirrhosis, toxic hepatitis and others. The question of surgery because of assumed extrahepatic biliary obstruction may arise. Liver biopsy is helpful, but may not be in the early stage in which inflammatory reactions are absent; later it may become more helpful but also more dangerous. 2. Drug-induced intrahepatic cholestasis: The drugs are arsphenamine, chlorpromazine, para-aminosalicylic acid, thiouracil, sulfanilamide, sulfadiazine, methyltestosterone, norethandrolone (Nilevar) and methimazole (Tapazole). In addition to cholestasis, inflammatory reaction and jaundice may or may not be present. 3. Idiopathic types: Possibly some of these are viral hepatitis, others possibly of endocrine origin. The microscopic pictures in the above groups, which may be practically pathognomonic, are illustrated by photographic reproductions and diagrams, but often even the pathologist expert in liver diagnosis cannot be of help and surgical exploration or pericutaneous cholangiography becomes necessary. A brief clinical description of the above groups is also included.

SAMUEL L. IMMERMAN

CLINICAL ASPECTS OF JAUNDICE RESULTING FROM INTRAHEPATIC OBSTRUCTION: F. W. Hoffbauer. J.A.M.A. 169:1453 (28 March), 1959.

The clinical types discussed are virus hepatitis, cirrhosis, and toxic liver injury. With cellular degeneration, the clinical picture, laboratory tests and biopsy are fairly distinctive. When cholestasis predominates, biopsy is then helpful since the same clinical picture may be produced by extrahepatic obstruction. Clinically the patient may have had jaundice for a long time; the laboratory signs of obstruction, increased bilirubin, increased alkaline phosphatase and increased lipids are present; but signs of liver cell damage, altered albumin/globulin and cephalin flocculation may be minimal. Yet, even here the experienced pathologist may be able to recognize the diagnosis by biopsy. On the other hand, in long-standing extrahepatic obstruction, cellular damage may also be present, and it may not be possible to resolve the mixed picture without x-ray visualization of the common duct or surgical exploration. Hoffbauer advises treating the patient medically for 4 to 6 weeks; this is a disadvantage for the patient who has surgical jaundice but may be lifesaving for the patient with medcal jaundice in whom surgical intervention is not only unrewarding but actually hazardous.

Chlorpromazine jaundice may develop 14 to 19 days after cessation of intake, even though the drug has been taken away for 5 or 6 days. The jaundice may last as long as 20 months. The prodromal symptoms re-

semble those of viral hepatitis, fever, malaise, anorexia, mild abdominal pain, and indefinite gastrointestinal symptoms for 3 or 4 days. The jaundice is typically obstructive with dark urine and light stools. In the next state, the prostration that usually accompanies virus hepatitis is absent; there is itching. The average duration of jaundice is weeks to 2 months. The laboratory tests are those of obstruction; the biopsy shows cholestasis and minimal inflammatory changes. In prolonged cases, the spleen may be enlarged.

Methyl testosterone jaundice can appear after some months of therapy and in a general way resembles chlorpromazine jaundice. If the drug is given to relieve itching of other types of jaundice, it usually increases the jaundice; and it may increase edema. Cortisone may decrease this, but may also cause gastrointestinal bleeding. An experienced pathologist may be able to make the correct diagnosis of methyltestosterone jaundice.

Primarily biliary cirrhosis usually occurs in middle-aged women. There is icterus, pruritus, melanotic pigmentation of the skin; sometimes xanthoma; a palpable, usually nontender liver. The disease is of long duration. The microscopic picture is said to be fairly distinctive. The earlier laboratory tests are those of obstruction; later of liver cell damage and portal hypertension. Skeletal demineralization and bone pain may be helped by calcium and Vitamin D. Operation for bleeding esophageal varices may need to be considered, and splenectomy if hypersplenism produces an important decrease of the blood-forming elements.

SAMUEL L. IMMERMAN

BOOK REVIEWS FOR GASTROENTEROLOGISTS

TROPICAL SPRUE, STUDIES OF THE U. S. ARMY SPRUE TEAM IN PUERTO RICO: Medical Science Publications No. 5, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C., 1958. Lt. Colonel William H. Crosby, M.D., Editor. 355 pages, illustrated. Obtainable from the Superintendent of Documents, Washington, D. C. Price $1.75.

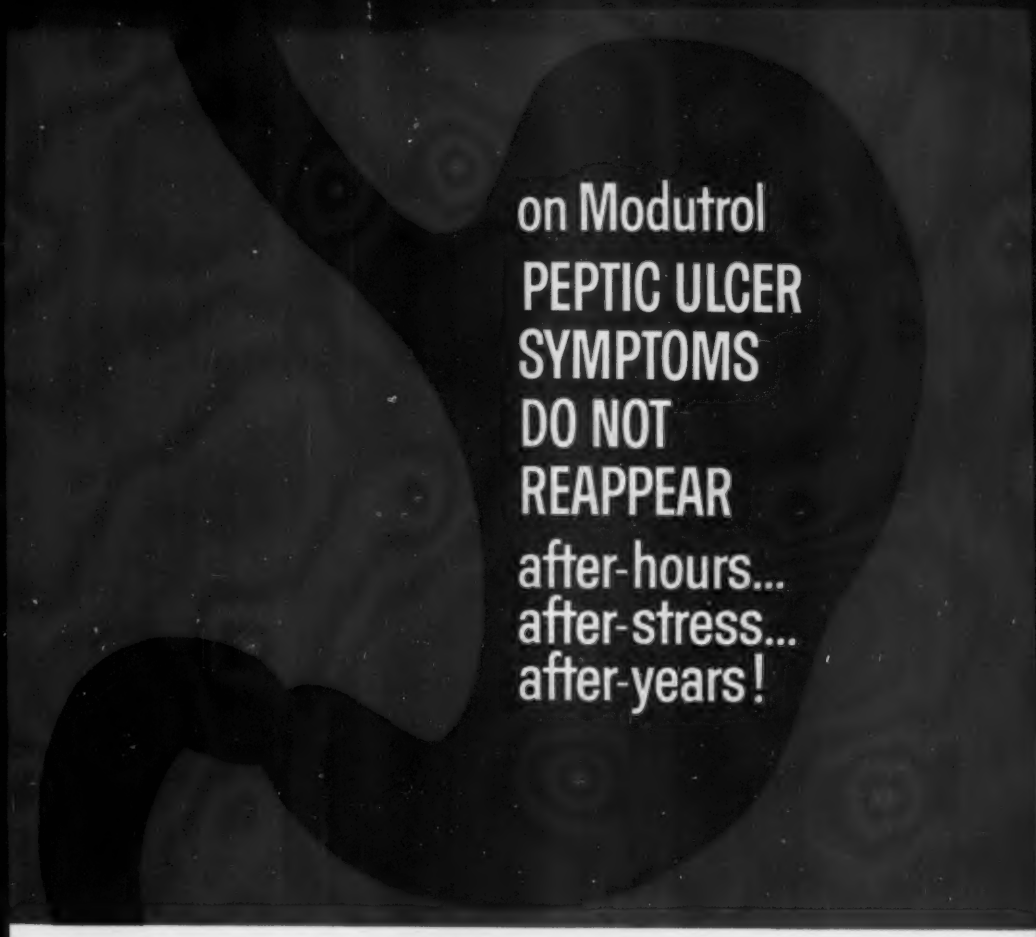
The results of the Army's Sprue Team in Puerto Rico are documented in this paperbound publication dealing with the investigation, treatment and results obtained by a group who began their investigation in 1953.

Physicians will find valuable suggestions, which may be applicable in some of their patients.

DISEASES OF METABOLISM, DETAILED METHODS OF DIAGNOSIS AND TREATMENT: Garfield G. Duncan, M.D., Professor of Medicine, University of Pennsylvania; Director of Medical Division, Pennsylvania Hospital and the Benjamin Franklin Clinic. Fourth Edition. 1104 pages, illustrated. W. B. Saunders Co., Philadelphia, Pa., 1959. Price $18.50.

Well known clinicians have contributed to make this an outstanding text on diseases of metabolism. The editor, Dr. Duncan, is well known in the field of metabolism, and that this volume has reached its fourth edition is a compliment to him.

All physicians are urged to purchase and read this book. They will learn about the great advances made in diagnosis and treatment.



Modutrol allows complete and *lasting freedom* from symptoms—without dietary restrictions. Of all agents tested, only Modutrol achieved the three rigid objectives for success in peptic ulcer therapy: relief of symptoms, healing of ulcer and prevention of recurrences or complications. Moreover, Modutrol met these criteria in over 96 per cent of all patients tested.[1]

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FORMULA: Each Modutrol tablet contains: Sycotrol (pipethanate hydrochloride) 2 mg., scopolamine methylnitrate 1 mg., magnesium hydroxide 200 mg., aluminum hydroxide 200 mg.

DOSAGE: One tablet 3 or 4 times daily.

SUPPLIED: Bottles of 50 and 100 tablets.

CONTRAINDICATIONS: Contraindicated in glaucoma because of its anticholinergic components.

1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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Unexcelled Therapeutic Response: Results of the Administration of Sorboquel Tablets[1-3]

		Response		
	No. of Patients	*Excellent*	*Good*	*Poor*
Chronic Diarrhea*	**485**	335	76	74
		84.7%		15.3%
Acute Diarrhea**	**332**	288	22	22
		93.4%		6.6%

*Chronic diarrheas include irritable bowel syndrome, regional enteritis, diverticulitis and ulcerative colitis, postantibiotic enteritis, malabsorption syndrome, radiation proctitis, surgically short-circuited intestinal states. Diarrhea had persisted for more than a year in a large percentage with bowel movement frequency averaging from 5 to more than 10 a day. In most patients, SORBOQUEL controlled the condition within 3 days, even where other agents had failed.

**Acute diarrheas include nonspecific gastroenteritis, enteritis, enterocolitis. Control of the diarrhea was achieved within 24 hours in most cases.

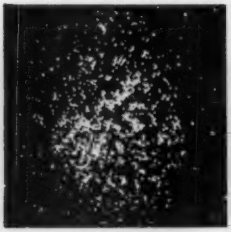
Dual-action **Sorboquel** arrests diarrhea even where all other agents have failed

The components in Sorboquel: the culmination of many years of development

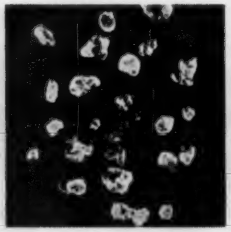
SORBOQUEL Tablets combine two unique and hitherto unavailable antidiarrheal agents—polycarbophil and thihexinol methylbromide. Acting together, through different but complementary mechanisms, these components in SORBOQUEL *absorb* free fecal water and *quell* hypermotility and associated spasm to an exceptional degree.

For too fluid feces, an extraordinary ability to absorb free fecal water

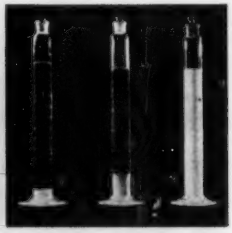
(through the hydrosorptive action of new polycarbophil)



Dry State
Demonstration of the particulate nature of dry polycarbophil.



Swollen State
Note the particulate nature of swollen polycarbophil. Impaction is virtually impossible.



(a) (b) (c)

Demonstration of the dependence of swelling of polycarbophil on pH (a) pH of stomach; (b) pH of duodenum; (c) pH of intestines.

A newly synthesized macromolecular substance exhibiting extraordinary capacity for absorption and retention of free fecal water[9-11] ■ the colloidal suspension is free-flowing, since, in the swollen or hydrated state, the particulate structure is retained[9] ■ exerts marked hydrosorptive action only on reaching the alkaline medium of the small intestine and colon ■ virtually free of impaction qualities ■ pharmacologically inert, not absorbed from the gut[12]

Convenient tablet form; simple, uncomplicated dosage schedule

SORBOQUEL DOSAGE: For older children and adults, initial dosage of one SORBOQUEL Tablet q.i.d. is usually adequate. Severe diarrheas may require six, or even eight, tablets in divided daily doses. (Dosages exceeding six tablets a day should not be employed over prolonged periods.) Many patients can be maintained on one to three tablets daily after the diarrhea is brought under control.

SIDE EFFECTS: The incidence of side effects at recommended dosage is negligible. (The usual precautions when using parasympatholytic agents should be observed. ***Complete information regarding the use of*** SORBOQUEL TABLETS ***is available on request.***

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For too frequent evacuations, superior, yet selective, antimotility action
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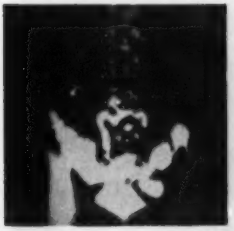
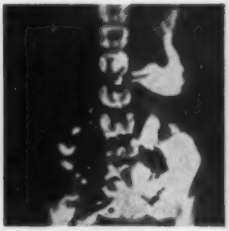
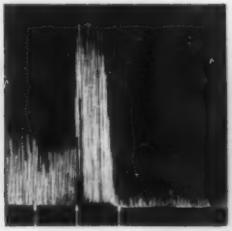


90-minute film demonstrating hypermotility of gastrointestinal tract in patient.



6-hour film after administration of thihexinol to patient showing marked inhibition of gastrointestinal motility.



(a) (b) (c)

Inhibition of methacholine-induced spasm by thihexinol in isolated rabbit intestine. Time of graph is 40 minutes. (a) normal motility; (b) methacholine, 40 mcg./L; (c) thihexinol, 10 mcg./ml.

A new, superior parasympatholytic agent with a dominant inhibitory action on intestinal motor function[12-16] ■ onset of intestinal motor inhibition has been shown to occur within *10-20 minutes*[14] ■ does not interfere with gastric secretion or digestive processes ■ unusually free from atropine-like side effects ■ its enteral antimotility action permits polycarbophil to exert maximal water-binding effect

SUPPLIED: SORBOQUEL TABLETS, bottles of 50 and 250. Each tablet contains 0.5 Gm. polycarbophil and 15 mg. thihexinol methylbromide.

REFERENCES: 1. Hock, C. W.: Med. Times 88:320 (March) 1960. 2. Winkelstein, A.: Personal communication. 3. Berkowitz, D.: in press. 4. Lind, H. E.: Personal communication. 5. Seneca, H.: in press. 6. Riese, J. A.: Personal communication. 7. Gilbert, A. S.; Schwartz, I. R., and Matzner, M. J.: Submitted for publication. 8. Personal communications to Medical Department, White Laboratories, Inc. 9. Pimparker, B. D.; Faustian, F. F.; Roth, J. L. A., and Bockus, H. L.: To be published. 10. Texter, E. C.: Personal communication. 11. Clinical reports to Medical Department, White Laboratories, Inc. 12. Grossman, A. J.; Batterman, R. C., and Leifer, P.: J. Am. Geriat. Soc. 5:187 (Feb.) 1957. 13. McHardy, G.; Browne, D.; McHardy, R.; Bodet, C., and Ward, S.: Am. J. Gastroenterol. 24:601 (Dec.) 1955. 14. Shay, H.: Personal communication. 15. Hirsh, H.: Personal communication. 16. Bercovitz, L. T.: J. Am. Geriat. Soc. 5:940 (Nov.) 1957.

WHITE LABORATORIES, INC., *Kenilworth, New Jersey*

containing Oxethazaine
a gastric mucosal
anesthetic

OXAINE*

Oxethazaine in Alumina Gel, Wyeth

for gastritis

an original development,
backed by 5 years' research
and clinical trial

*Trademark

OXAINE contains a gastric mucosal anesthetic for the relief of pain of gastritis.

OXAINE is indicated in the many patients who do not respond to diet, antacids and anticholinergics.

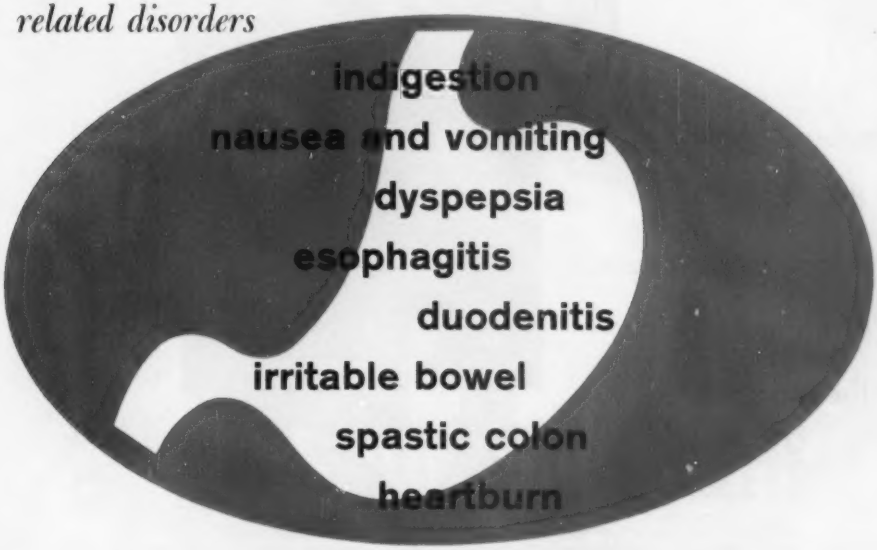
As reported in J.A.M.A., OXAINE brought complete relief to 96% of 92 gastritis patients suffering substernal pain and upper abdominal distress.
Deutsch, E., and Christian, H.J.: J.A.M.A. 169:2012 (April 25) 1959.

OXAINE provides sustained anesthesia over many hours, unaffected by ebb and flow of gastric contents.

Oxethazaine, the mucosal anesthetic in OXAINE, is 4000 times more potent topically than procaine. Safe, not a "caine." Only two known cases of sensitivity (glossitis) occurred in extensive clinical trials.

Easily administered, simple dosage—just 2 teaspoonfuls 15 minutes before meals and at bedtime. Bland, noncloying over long-term administration.

related disorders



How OXAINE Relieves Pain, Hastens Recovery

Gastric mucosa can heal more quickly, because local anesthetics inhibit acid and pepsin secretion, by preventing release of *gastrin* from the antrum of the stomach.

Patients tolerate a more varied diet and a larger amount of food—and, because of OXAINE, enjoy their food without fear of pain following meals.

They feel free of bloating and the disturbing sensation of fullness when only a little food has been ingested—because the anesthesia of OXAINE desensitizes irritated nerve receptors.

Supplied: *In bottles of 12 fluidounces.*

Wyeth Laboratories Philadelphia 1, Pa.

Those with irritable bowel syndrome are spared the embarrassing urge to defecate during meals—because OXAINE diminishes the exacerbated gastrocolic reflex.

For further information on prescribing and administering OXAINE see descriptive literature, available on request.

Wyeth

A Century of Service to Medicine

the battle won in the shipping department... is often lost in the stomach

Shipping clerk, age 23, complained of mid-epigastric night pain that was relieved by the ingestion of food. The patient also suffered from "indigestion," occasional nausea and vomiting, and a feeling of tension.

Once before, the patient had been placed on t.i.d. anticholinergic therapy for epigastric pain, but had failed to maintain the prescribed regimen.

A g.i. series showed a duodenal ulcer.

A q12h 'Combid' *Spansule* capsule regimen plus antacid therapy was prescribed. He was put on a bland diet. One week later the patient reported that he was symptom-free. He has continued to take 'Combid' *Spansule* capsules prophylactically and has remained free from g.i. distress.

SMITH KLINE & FRENCH

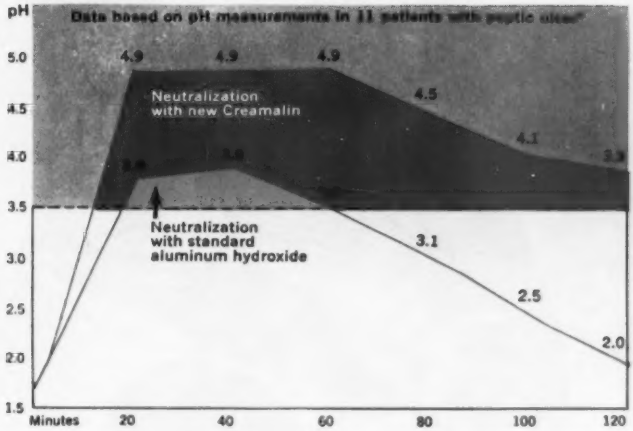
Combid® b.i.d.
brand of prochlorperazine and isopropamide

Spansule®
brand of sustained release capsules

Smith Kline & French Laboratories, Philadelphia

At the site of peptic ulcer

Following determination of basal secretion, intragastric pH was continuously determined by means of frequent readings over a two-hour period.



neutralization is much faster and twice as long with

New CREAMALIN® ANTACID TABLETS

New proof in vivo[1] of the much greater efficacy of new Creamalin tablets over standard aluminum hydroxide has now been obtained. Results of comparative tests on patients with peptic ulcer, measured by an intragastric pH electrode, show that new Creamalin neutralizes acid from 40 to 65 per cent faster than the standard preparation. This neutralization (pH 3.5 or above) is maintained for approximately one hour longer.

New Creamalin provides virtually the same effects as a liquid antacid[2] with the convenience of a tablet.

Nonconstipating and pleasant-tasting, new Creamalin antacid tablets will not produce "acid rebound" or alkalosis.

Each new Creamalin antacid tablet contains 320 mg. of specially processed, highly reactive, short polymer dried aluminum hydroxide gel (stabilized with hexitol) with 75 mg. of magnesium hydroxide. Minute particles of the powder offer a vastly increased surface area for quicker and more complete acid neutralization.

Dosage: Gastric hyperacidity — from 2 to 4 tablets as necessary. Peptic ulcer or gastritis — from 2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed whole with water or milk, or allowed to dissolve in the mouth. **How supplied:** Bottles of 50, 100, 200 and 1000.

1. Data in the files of the Department of Medical Research, Winthrop Laboratories. 2. Hinkel, E. T., Jr.; Fisher, M. P., and Tainter, M. L.: J. Am. Pharm. A. (Scient. Ed.) 48:384, July, 1959.

Winthrop LABORATORIES
New York 18, N. Y.

for peptic ulcer ■ gastritis ■ gastric hyperacidity

Life's Handicap
The Courting of Dinah Shadd
—Rudyard Kipling

"Glory's no compensation for a belly-ache."

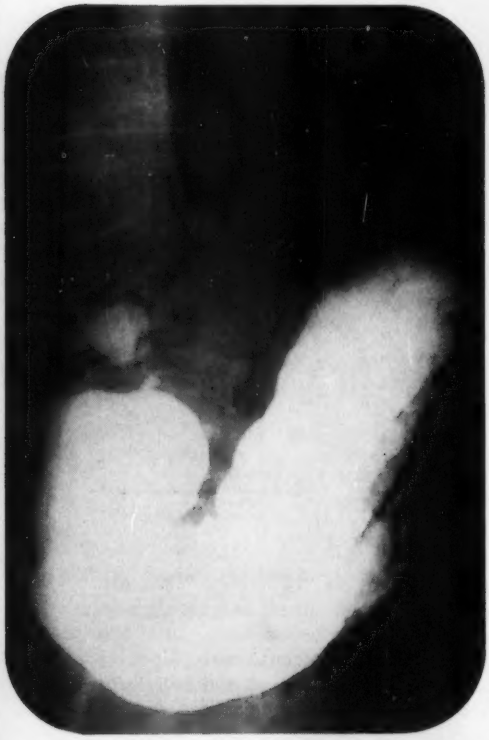
Hardly anything compensates for the misery attendant to "belly-ache," pyrosis, belching, and flatulence that result from food intolerance or simple overindulgence. But Entozyme can do much to help prevent or alleviate such symptoms, for it is a natural supplement to digestive enzymes, providing components with digestive enzyme activity: *Pepsin*, N. F., 250 mg., *Pancreatin*, N. F., 300 mg., and *Bile Salts*, 150 mg. Because Entozyme is actually a tablet-within-a-tablet, its components are freed in the gastrointestinal areas where they are therapeutically most effective. Entozyme has proved useful in relieving many symptoms associated with cholecystitis, post-cholecystectomy syndrome, sub-total gastrectomy, pancreatitis, infectious hepatitis, and a variety of metabolic diseases.

A. H. ROBINS CO., INC.
RICHMOND 20, VA.

ENTOZYME®

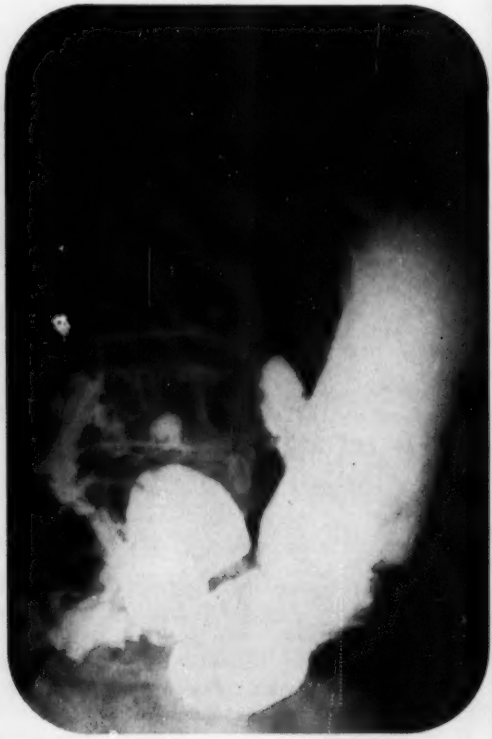
EFFECTIVENESS OF "MUREL"-S. A. IN SPASM VISUALLY CONFIRMED

55 year old male with symptoms of partial obstruction of the stomach; nausea and vomiting.



March 1st, 1960: Large dilated stomach with incomplete pyloric obstruction. Etiology undetermined.

Patient placed on "Murel"-S.A. — 2 tablets b.i.d. for one week — plus bland diet. No other medication.



March 10th, 1960: Stomach of normal size and tone. Large ulcer crater now visualized in the region of previously noted pyloric spasm and incomplete filling.

Medical Records of Ayerst Laboratories

in G.I., G.U. and Biliary SPASM

"Murel"-S.A.

Sustained Action Tablets

prompt, continuous and prolonged antispasmodic action for 6 to 9 hours with a single tablet

"MUREL" Advantages[1-4]

- Exceptionally effective clinically because three-way mechanism of action in one molecule (anticholinergic, musculotropic, ganglion-blocking) exerts synergistic spasmolytic effect
- Complementary action permits significantly low dosage and reduces reaction potential of any one mechanism
- Remarkably free from drug-induced complications such as mouth dryness, visual disturbances, urinary retention

Suggested Average Dosage: 40 to 80 mg. daily, depending on condition and severity. The higher range of dosage is usually required in spasm of the genitourinary and biliary tracts. One "Murel"-S.A. Sustained Action Tablet morning and evening. *When anxiety and tension are present,* "Murel" with Phenobarb-S.A. is suggested.

Available as: No. 315—"Murel"-S.A., 40 mg. Valethamate bromide; and No. 319—"Murel" with Phenobarb-S.A., with ½ gr. phenobarbital, present as the sodium salt. Both in bottles of 100 and 1,000.

Also available: "Murel" Tablets No. 314—10 mg. Valethamate bromide; "Murel" with Phenobarbital Tablets No. 318—10 mg. Valethamate bromide and ¼ gr. phenobarbital.

"Murel" Injectable No. 405—10 mg. Valethamate bromide per cc.

Precautions: As with other antispasmodic agents, caution should be exercised in patients with prostatic hypertrophy, glaucoma, and in the presence of cardiac arrhythmias.

References available on request.

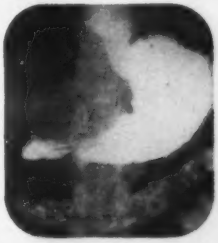
Ayerst

AYERST LABORATORIES
New York 16, N.Y. • Montreal, Canada

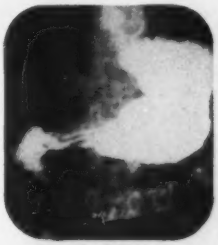
for acute, severe episodes
"MUREL" Injectable

Female patient, age 55, complaining of nausea and epigastric discomfort after meals.

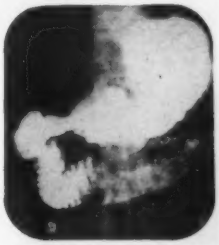
Diagnosis: Hiatus hernia and gastric ulcer.



1 hour after barium administration: Retention of barium due to spasticity of the gastric outlet, and incomplete visualization of the pylorus, duodenum and duodenal sweep. (Some barium has entered the small bowel.)



20 minutes after administration of "Murel" 2 cc. I.V.: Barium entering duodenum and duodenal sweep as spasticity is relieved.



10 minutes later: Good filling of the gastric outlet as well as of the duodenal sweep.

Medical Records of Ayerst Laboratories 6037

" . . . Well, I always prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients will take it indefinitely."

. . . . . .

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

TABLET MAALOX No. 2: 0.8 Gram, double strength (equivalent to two teaspoonfuls), Bottles of 50 and 250.

Samples on request.

WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.